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THE DIAGNOSIS OF CORONARY-ARTERY DISEASE*

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IT IS surely unnecessary to remind an audience composed of physicians that the many factors that may enter into the diagnosis of coronary-artery disease cannot possibly be discussed in any adequate or comprehensive fashion in the space of a few minutes, or indeed of a few hours. I am sure that I shall be forgiven if I attempt to present in abbreviated and almost tabular form a few of the more important established facts relating to this condition. Any appearance of dogmatism or unjustified authority in my statements is due solely to limitations of time, which do not permit the discussion of controversial points or the presentation of opposing evidence.

The term "coronary-artery disease" so widely used today includes all known varieties of change in these vessels, and some of them are so infrequent or of such slight clinical interest as to justify their exclusion. In general, ability to recognize disease of the coronary arteries is restricted to conditions that interfere with the nutrition of the myocardium sufficiently to cause symptoms, changes in the x-ray film or alterations in the electrocardiogram. Changes of this degree are usually due to arteriosclerosis, with narrowing or closure of coronary branches, and I interpret the term "coronary-artery disease" to mean coronary arteriosclerosis for the purposes of this discussion. And the question that I shall attempt to answer, in part, is, What criteria will enable one to suspect, or to recognize with certainty, structural changes in the coronary arteries that interfere with the heart's nutrition sufficiently to be of consequence to the patient?

Clinical Evidence

There is now complete agreement among authorities that the presence of typical and unmistakable anginal pain should be regarded as evidence that the coronary blood flow is inadequate for the needs of the heart muscle, and that this inadequacy is due in most cases to arteriosclerotic narrowing or closure of the vessels, although typical anginal pain may occur in the presence of normal coronary arteries in cases of severe anemia or during prolonged paroxysms of tachycardia with excessive ventricular rates. It may also occur in the absence of coronary arteriosclerosis in occasional cases of hyperthyroidism, or in patients whose hearts are greatly enlarged as a result of hypertension or rheumatic disease of the aortic valves, presumably because the increased demands of the hypertrophied myocardium for blood are not met by a corresponding increase in the coronary blood flow.

The question that immediately arises is, What *is* typical and unmistakable angina? Most cardiologists frequently encounter patients whose physicians have assured them that they have angina pectoris, when a careful analysis of their symptoms reveals that they do not. The diagnosis of angina is based, with one possible exception, exclusively on the history given by the patient, and not in any degree on the physical or x-ray examination, or the electrocardiogram. And the history that compels a diagnosis of angina includes among its more significant features the following: the discomfort in the chest is dull, squeezing or constricting, never sharp or knifelike; it occurs usually beneath the sternum, and not over the body of the heart; if it radiates, it is almost always to the shoulder and down the inner aspect of the arm, more frequently the left; the discomfort is of brief duration, usually from half a minute to three or four minutes; it is constant from the moment of onset until its complete disappearance — that is, it does not come and go, or wax and wane in intensity, for periods of seconds; it has a close rela-

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tion to factors that impose greater work on the heart, the most important being physical effort and emotional excitement; the discomfort is quickly relieved by rest, is abolished even more speedily in most cases by nitroglycerin, and is prevented if nitroglycerin is administered in advance of the effort that usually provokes it. If all or most of these characteristics are present, one *must* make a diagnosis of angina; if many of them are lacking, one must suspect that the discomfort is probably not due to abnormality of the heart. If anginal pain is present in the absence of anemia, hyperthyroidism and rheumatic heart disease, it is almost certain that coronary arteriosclerosis exists, and highly probable that complete occlusion of one or more arteries has occurred. In a recent study of great value, Blumgart, Schlesinger and Davis[1] report that, in 12 cases of angina, autopsy disclosed old complete occlusion of all three main coronary arteries in 3, and old complete occlusion of two main arteries in 7. In the remaining 2 cases of the group, one main artery was completely closed by an old thrombotic process, and the other two were greatly narrowed by arteriosclerosis. In other words, in 12 patients with typical angina pectoris, twenty-five main coronary arteries (out of the total of thirty-six) had been closed by thrombus formation months or years before death.

The occurrence of acute myocardial infarction must be regarded as almost certain evidence that disease of the coronary arteries is present, since embolic occlusion of these vessels is rare. This is so obvious and so widely accepted by experienced observers that it need only be mentioned. I shall not discuss the diagnostic features of this condition, but one must remember that the electrocardiogram frequently discloses the typical signs of acute or old myocardial infarction when the history is merely that of rather mild anginal pain, without any acute episode to suggest when the arterial closure occurred.

Furthermore, one must assume that narrowing or closure of the coronary arteries has occurred if congestive heart failure is present in the absence of the other usual causes. These other causes, of course, include rheumatic, syphilitic and hypertensive heart disease, vitamin B deficiency and diseases of the pericardium, especially the form that leads to chronic constrictive pericarditis. If these can be excluded, congestive heart failure may be confidently ascribed to diminished coronary blood flow, with consequent impairment of the nutrition of the heart muscle and often with fibrotic changes in the myocardium. This form of heart disease is widely known as arteriosclerotic heart disease, and I wish merely to emphasize the fact that the term "arteriosclerotic" in this designation refers to the coronary arteries and not to those elsewhere in the body.

The clinical evidence that points to coronary arteriosclerosis may be summarized as consisting of a clear history of anginal heart failure in the absence of the other infrequent causes, the occurrence of acute myocardial infarction, or the presence of congestive heart failure if other types of heart disease and vitamin deficiency can be excluded.

Roentgenologic Evidence

Concerning x-ray evidence, only a few matters seem worthy of mention. Actual calcification of the coronary arteries can be demonstrated occasionally by fluoroscopy or in the roentgenogram, but this is so relatively infrequent with present technics that it must be regarded as a sign of limited value. When present, it is visible proof that the vessels are sclerotic.

The presence of a ventricular aneurysm is now generally accepted as evidence that myocardial infarction has occurred. If the aneurysm is of considerable size, its recognition by means of fluoroscopy or films is not difficult, but in my opinion the diagnosis is frequently not easy, is often made on insufficient evidence, and the simplicity of the diagnosis has been overemphasized by some writers.

About a year ago, Master and his colleagues[2] published their observations on the diagnosis of coronary-artery occlusion and myocardial infarction by means of fluoroscopic examination. They noted localized abnormalities in pulsation of the ventricle in 73 per cent of their 80 cases of myocardial infarction and in 2 of their 15 patients who had angina pectoris, without a history suggestive of coronary occlusion. The abnormalities in pulsation consisted largely of localized diminution in the movement of the ventricular wall, absence of movement or actual reversal of pulsation. If a portion of the ventricular wall moves outward (systolic expansion) while the rest of the wall moves inward, this is thought to be pathognomonic of myocardial infarction unless the heart is considerably enlarged. The abnormalities detected by fluoroscopic examination corresponded closely with those noted in roentgen kymograms taken immediately afterward. It is believed that these changes in contraction may be permanent and not confined to the period of acute injury or convalescence.

I am frankly uncertain of the value of this method as a purely diagnostic procedure when employed by clinicians, as distinguished from roentgenologists. But there can be no question

that the signs described by Master and his colleagues are present in a number of patients who have sustained myocardial infarction; they are often overlooked because the examiners are not aware of the possibility that localized reversal of pulsation may occur, or because insufficient time is given to the examination. On a few occasions, one of my colleagues has pointed out this sign during the fluoroscopic examination of patients whose histories and diagnoses were entirely unknown to him. In every case, the history and electrocardiogram indicated clearly that myocardial infarction had occurred. The sign should be kept clearly in mind during the fluoroscopic examination of all patients who are suspected of having sclerosis of the coronary arteries.

The roentgenologic evidence may be summarized with the statement that coronary arteriosclerosis is present if calcification of the vessels can be demonstrated, if there is a ventricular aneurysm, or if localized reversal of ventricular pulsation is revealed by fluoroscopic examination.

Electrocardiographic Evidence

Changes in the electrocardiogram that have been, and are still being, interpreted as indications of coronary arteriosclerosis are so numerous that I must arbitrarily select only a few of them for brief discussion. I shall speak of four.

The first of these is the widening and notching of the chief ventricular deflection commonly known as intraventricular block or bundle-branch block. When this is found, many physicians do not hesitate to assert positively that coronary arteriosclerosis is present and is responsible for the change in the QRS group. This assertion seems to me quite unjustifiable. The impressive change in the electrocardiogram, although it undoubtedly means heart disease in most cases, may occur in the rheumatic and syphilitic types at an age when coronary sclerosis is very unusual and is presumably absent. It is frequently observed in diphtheritic myocarditis in young children. In some cases, the change is due to digitalis, and may be made to appear and disappear at will by the administration or omission of this drug. It has been found in a small group of young healthy people, including splendid athletes, who present no other signs of heart disease and whose hearts are thought by competent authorities to be normal. Bundle-branch block has also been observed in a few patients in whom careful post-mortem examination revealed no lesions in the coronary arteries or the myocardium. It seems reasonably clear, therefore, that even so dramatic a change as bundle-branch block cannot be regarded as having a specific meaning but, like almost all other changes in the curve, must be interpreted in the light of the clinical findings.

Low voltage of the ventricular deflections in all leads, in the absence of any other abnormality in the record, has often been regarded as an unmistakable sign of widespread myocardial change, and many still interpret this finding as a specific sign of coronary atherosclerosis. That this is not necessarily true is perhaps indicated sufficiently by the fact that low voltage has been reported by leading authorities as occurring in hypothyroidism, rheumatic or syphilitic heart disease, leukemia, pericardial effusion, adhesive mediastinopericarditis, emphysema, chronic nephritis with renal failure, and many acute or chronic infections not involving the heart. In a recent report, Barritt[3] states that of 36 patients whose curves showed low voltage of the QRS group but upright T waves, 20 had no clinical signs of heart disease. Leach, Reed and White,[4] in a study of 300 cases showing low voltage of the QRS complexes in the limb leads alone, in the precordial lead alone or in all four leads, found evidence of heart disease in only 57 per cent of the entire group. They state that heart disease was of no greater relative significance than extracardiac factors in cases showing extreme reduction in voltage (to 0.3 millivolts or less). Ten per cent of the entire group were apparently normal and healthy in every respect. They conclude that the solitary finding of low voltage is of little or no value as an indication of the presence or absence of heart disease or of any other trouble.

A large Q wave in Lead 3 has aroused a good deal of discussion in recent years because of the belief that it is often associated with angina pectoris or other manifestations of coronary atherosclerosis. It is not possible to present the very considerable evidence relating to the significance of this wave, and I must therefore make a rather arbitrary statement of my own belief. It is fairly certain that in some cases a deep Q wave in Lead 3 is the sole remaining sign of old infarction of the posterior wall of the left ventricle, but it is likelier to have this significance if there is also a Q wave in Lead 2. But, on the basis of reported studies and my own experience, I am convinced that large Q waves are present in Lead 3 of many normal subjects and are of no diagnostic or prognostic consequence in such cases. I believe that these waves are not uncommon in normal obese people whose diaphragms are rather high and whose hearts are consequently placed more transversely than normal. Not infrequently, the T wave in this lead is inverted when the Q wave is large. Both the large Q wave and the inversion of

the T wave may disappear if the curve is recorded during deep inspiration or while the subject stands erect. Both the deep Q and the inverted T waves may remain for many years without change and without the appearance of any signs of heart disease. I have little hesitation, therefore, in expressing the opinion that it is unjustifiable and even deplorable to interpret a deep Q wave in Lead 3 by itself as an indication of heart disease, and especially as a specific sign of coronary sclerosis.

And, finally, I come to that portion of the curve that has caused greater trouble than all others combined: the ST segment and T wave. I cannot discuss this in the detail that it merits. Depression or elevation of the ST junction or segment and inversion of the T wave are apparently more generally accepted than any other changes in the electrocardiogram as indications of heart disease, and especially of coronary arteriosclerosis. Whether or not this statement is justified can be judged by the following quotation from a recent article by Sprague[5]:

> Without the hope of its being complete, the following list of conditions, other than coronary atherosclerosis, responsible for abnormalities of S-T and T segments is submitted:
>
> 1. Drugs
> *a.* Digitalis
> *b.* Quinidine
> *c.* Tobacco
> 2. Myocardial infection
> *a.* Rheumatism
> *b.* Diphtheria
> *c.* Trichinosis
> 3. Other general infections
> *a.* Pneumonia
> 4. Pericarditis
> 5. Toxemia and metabolic disorders
> *a.* Uremia
> *b.* Diabetic acidosis
> *c.* Hypocalcemia
> *d.* Hyperthyroidism
> *e.* Hypothyroidism
> *f.* Insulin shock
> *g.* Addison's disease
> *h.* Anemia
> *i.* Avitaminosis, especially beriberi
> *j.* Acidosis
> *k.* Alkalosis
> *l.* Anoxemia
> *m.* Shock
> 6. Changes in posture of the patient
> 7. Axis deviation
> 8. Abnormal heart rhythms
> *a.* Paroxysmal tachycardia and auricular fibrillation
> *b.* Sinus tachycardia
> 9. Alterations in vago-sympathetic tone
> *a.* Pain
> *b.* Fear
> *c.* Anesthesia
> 10. Pulmonary embolism
> 11. Miscellaneous
> *a.* Periarteritis nodosa
> *b.* Trauma
> *c.* Malignancy of myocardium
> *d.* Dissecting aneurysm of coronary artery
> *e.* Dissecting aneurysm of aorta
> *f.* Syphilis of aorta
> *g.* Gall bladder disease
> *h.* Scleroderma
> *i.* General anasarca
> *j.* Cooling the heart through ingestion of ice water
> *k.* Terminal states of all kinds
> *l.* Unexplained

This list contains forty-one different conditions, thirty-three of which do not imply heart disease!

I do not wish to imply that coronary atherosclerosis does not cause changes in the ST segments and T waves, because undoubtedly it does. But I do wish to state emphatically that coronary disease is only one of many factors that cause such changes, and it is impossible to decide from the electrocardiogram alone which of these many causes is responsible. One might just as well attempt to make a correct and specific diagnosis of disease on the sole basis of slight leukocytosis, without any knowledge of the clinical picture and other laboratory tests.

I think that this whole matter may be summarized in one sentence. If myocardial infarction is excluded, *there is no change in the electrocardiogram that in itself justifies the diagnosis of coronary disease*, because the alterations on which this diagnosis is based may be — and often are — due to other causes. I am in the heartiest agreement with Wilson[6] when he says, "It would be better if this term [coronary disease] were never used under any circumstances in connection with the interpretation of the electrocardiogram."

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ABDOMINOSCROTAL HYDROCELE*

Review of the Literature and Report of a Case

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BOSTON

ABDOMINOSCROTAL hydrocele represents an unusual type of the extremely common condition known as hydrocele. Since the first description by Dupuytren[1] in 1834, when the term *l'hydrocèle en bissac* was used, numerous titles have been applied to the condition. "Bilocular abdominal hydrocele" has been employed by a number of German authors,[2-7] presumably because the large abdominal and scrotal compartments are sometimes connected by an isthmus-like constriction. Lister,[8] interested by the extraordinary clinical appearance of a patient, did a post-mortem dissection of the large abdominoscrotal sac and published his results in 1856. Another of the early descriptions was given in 1853 by Fano,[9] a prosector of the faculty of medicine of Paris. "Abdominal hydrocele" was the descriptive term given by Steele[10] in 1875 and by Trendelenburg[11] in 1877. "Intraabdominal hematocele" was used by Tillmanns,[12] and "hydrocele bilocularis" by Witzel[13]; in 1887, Kocher[14, 15] combined the terms in his text, using "intra-abdominal bilocular hydrocele and hematocele." In the same year, Bazy[16] published an article with illustrations, under the title "Vaginal Hydrocele with Abdominal Prolongment." Villeneuve[17] wrote a brief review of the subject in 1890. Jacobson,[18] whose classification of the types of hydrocele is still used today, described the malady as "infantile hydrocele with prolongation into the abdomen" in his textbook published in 1893. Such variations of terminology continued until Bickle,[19] in 1919, reviewing a paper that he[20] had published in 1902, suggested "abdominoscrotal hydrocele" as a proper descriptive title. Although only a few papers have been published on this subject since that time, Bickle's suggestion appears to have been accepted. It seems more generally applicable than the term "properitoneal hydrocele" recommended by Holmes[21] in 1932.

As the term indicates, an accumulation of fluid in the cavity of the tunica vaginalis causes scrotal enlargement and extends through the region of the inguinal canal into the abdomen or iliac fossa. The abdominal part of the hydrocele — as well as the scrotal part — is, of course, extraperitoneal and may reach rather large proportions. Lasbrey[22] recovered 2700 cc. (90 ounces), and von Winiwarter[5] stated that he withdrew 7000 cc. from the mass in one patient. A quantity of liquid of this extent in the abdomen naturally produces a startling pic-

FIGURE 1. *Drawing of an Abdominoscrotal Hydrocele (Bazy[16]).*

ture not unlike the abdominal distention caused by a pregnancy of six or seven months. A drawing in Bazy's[16] article illustrates these remarks (Fig. 1).

To understand the development of the abdominoscrotal type of hydrocele, one must briefly review the anatomic development of the commoner vaginal, or simple, hydrocele. According to embryologic texts,[23] while the testes are still within the abdomen, a peritoneal projection or prolongation known as the processus vaginalis extends through the inguinal region over the pubis to the scrotum. The testes, descending to the scrotum posterior to and becoming partially invested by the peritoneum of the processus vaginalis, thus form a visceral and parietal layer of the tunica vaginalis in the scrotum. The stalk — or the portion of the processus vaginalis between the internal inguinal ring and the upper border of the testicle — normally becomes obliterated, separating the cavity of the tunica vaginalis from the peritoneal cavity.

Several types of hydrocele are shown in Figure 2. If fluid accumulates in the cavity of the tunica vaginalis and the stalk has closed normally as

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just described, a condition of simple vaginal hydrocele (ordinary hydrocele) exists. This is shown in Figure 2*A* by a diagram similar to those of Jacobson[18] and Campbell.[24] If the distal portion of the stalk of the processus vaginalis fails to become obliterated, so that the cavity of the tunica vaginalis extends upward to the level of the inguinal canal instead of to a point just above the testis, and if that cavity becomes filled with fluid, there exists, as originally outlined by Jacobson, an infantile type of hydrocele (Figs. 2*B* and 3). If the processus vaginalis becomes obliterated for only a very short distance at the level of the internal inguinal ring, and if a large amount of hydrocele fluid accumulates, further stretching of the sac toward the abdomen can occur, producing the condition known as abdominoscrotal hydrocele (Fig. 2*C*).

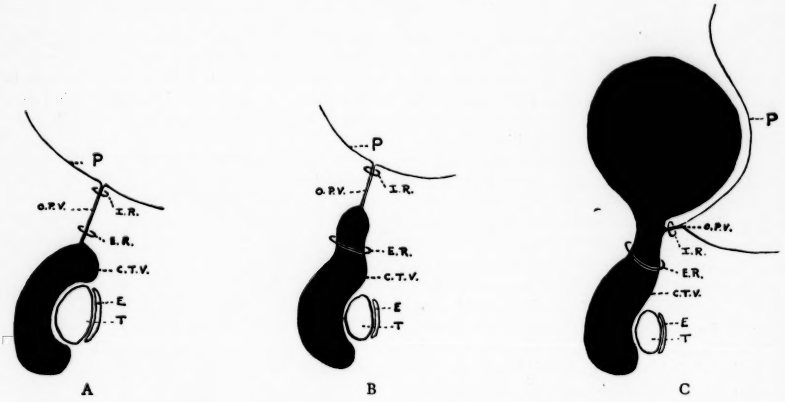

FIGURE 2. *Diagrams of Several Types of Hydrocele.*

A. — *Simple or vaginal hydrocele;* B. — *infantile hydrocele;* C. — *abdominoscrotal hydrocele. Abbreviations:* P. — *peritoneum;* E. — *epididymis;* T. — *testis;* I.R. — *internal inguinal ring;* E.R. — *external inguinal ring;* O.P.V. — *obliterated processus vaginalis;* C.T.V. — *cavity tunica vaginalis.*

FIGURE 3. *Drawing of the Infantile Type of Hydrocele (Bazy[16]).*

Several different theories have been held regarding the development of abdominoscrotal hydrocele and its relation to the peritoneum. Dupuytren[1] believed that with extreme distention the ordinary vaginal hydrocele could push its way up through the inguinal canal and assume an abdominal position. Kocher[14, 15] shared this view. Against the views of Dupuytren and Kocher may be cited the numerous cases of ordinary hydrocele in which the fluid is confined under considerable pressure, without extension beyond the confines of the simple vaginal hydrocele. Probably, the more logical explanation — expressed by Jacobson,[18] Macewen[25] and Tanzer,[26] with whom I agree — is that a persistent type of high infantile hydrocele exists in which the processus vaginalis is obliterated only at the level of the internal ring. If distention of the upper portion of the sac occurs, there are no confining structures on the posterior or peritoneal aspect to limit the abdominal expansion. As Tanzer has stated, the abdominal sac can be considered an evagination from the proximal end of the hydrocele sac (Fig. 2*C*).

The relation of the sac to the peritoneum and the abdominal wall deserves discussion. From the case reports, it becomes obvious that several types of abdominoscrotal hydrocele exist. In fact, Delbet,[27] in 1896, proposed that they be divided into properitoneal, interstitial and superficial types, on

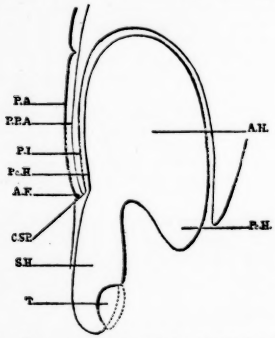

FIGURE 4. *Diagram of Layers of the Abdominal Wall and Peritoneum and Their Relation to an Abdominal Hydrocele (Bazy[16]).*

Abbreviations: P.A. — *abdominal wall;* P.P.A. — *peritoneum covering abdominal wall;* P.I. — *peritoneum covering iliac fossa, compressed by tumor;* Pa.H. — *wall of hydrocele;* S.H. — *scrotal portion of hydrocele;* A.H. — *abdominal portion of hydrocele;* Pe.H. — *pelvic portion of hydrocele;* A.F. — *femoral arch;* C.S.P — *peritoneal cul-de-sac;* T. — *testicle.*

the basis of the relation to the abdominal wall. To make this classification complete, one should add the retroperitoneal type. Bazy believed that there were two layers of peritoneum between the abdominal wall and the hydrocele sac (Fig. 4) and Lister,[8] after a post-mortem dissection on a case, declared that "it formed a tumor beneath the peritoneum lying in the iliac fossa and the lower part of the anterior wall of the abdomen." Coleman[28] also considered his case to be of the retroperitoneal type. On the other hand, Delbet believed that his case was of the superficial type, the sac lying superficial to the muscles of the abdominal wall. The majority of cases are, I believe, of the properitoneal type, in which the abdominal portion of the sac lies between the muscles of the abdominal wall and the peritoneum (Fig. 5).

The clinical aspects of abdominoscrotal hydrocele are of interest since the occurrence is relatively uncommon, and most communications on the subject consist of single case reports.[29–40] Some of the present-day texts on urology fail to mention the condition, although others[41, 42] briefly describe it. If Brandenburg[43] is correct in estimating the cases collected up to 1921, there have now been about 53 reported cases (including the one described in this paper)

The majority of patients were in the second or third decade of life when they sought treatment, although Kocher reported cases in children one and thirteen years old, and Syme[44] reported a case in a four-year-old child. The oldest men described in the case reports were the fifty-four-year-old patient of Fuchs[8] and the fifty-five-year-old patient of Wettergren.[45]

Both right and left scrotal regions have been affected and with approximately equal frequency. The history is usually that of a painless swelling developing first in the scrotal region and later extending to the groin and abdomen. Many patients are apparently not inconvenienced by the large abdominal protrusion that develops, although Steele's[10] patient complained of difficulty in walking. However, the symptoms in Steele's case may have been due to the pressure on an undescended testis rather than to the abdominal swelling per se.

Physical examination discloses not only the scrotal swelling but an abdominal tumor that can

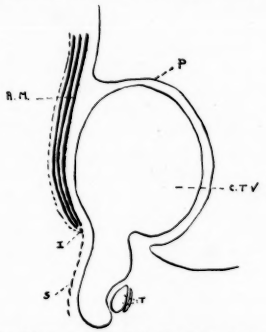

FIGURE 5. *Diagram of the Relation of the Peritoneum and Abdominal Muscles to an Abdominoscrotal Hydrocele.*

Abbreviations: A.M. — *abdominal muscles;* P. — *peritoneum;* C.T.V. — *cavity of tunica vaginalis;* I. — *level of inguinal ligament;* S. — *scrotal wall;* T. — *testis and epididymis.*

reach large proportions. It is not unusual to find the abdominal protrusion, the size of a six or seven months' gravid uterus, extending above the level of the umbilicus and beyond the midline. The tumor is smooth, firm, nontender and flat to percussion. The scrotal tumor transilluminates well unless the sac contains blood. Pressure on the abdominal portion of the sac creates a fluid wave or thrill to the scrotal area. Usually, coughing creates a definite impulse in the scrotal region, a phenomenon similar to the fluid wave produced by sudden compression of the abdominal portion of the sac. Occasionally, the abdominal swelling is extensive enough to give the impression of ascites. Catheterization of the bladder obviously fails

to reduce the size of the tumor. In the pelvic type of abdominoscrotal hydrocele, rectal examination should disclose a ballotable pelvic mass continuous with the scrotal swelling. Holmes[21] injected 60 cc. (2 ounces) of saturated sodium iodide into the scrotal sac before operating, and obtained a graphic picture of the large abdominoscrotal sac. It is evident that the diagnosis is not difficult so long as one realizes that such a condition exists.

Several different forms of treatment have been used. They may be grouped in three divisions: puncture, incision and drainage, and excision.

In 1860, Rochard[46] found it necessary to incise and drain a hematocele sac of 2940 cc. after the injection of iodine had been unsuccessful in the treatment of the condition. In 1875, Steele[10] tapped and withdrew 900 cc. (30 ounces); he then allowed infection to occur, hoping to obliterate the cavity by this method, and the incisions finally healed. Trendelenburg[11] likewise used incision and drainage. Kocher employed puncture in 2 children and followed the procedure by the injection of tincture of iodine in 1; phlegmon of the scrotum developed in 1 of these cases. Witzel[13] used for drainage a groin incision rather than one over the scrotum. In 1896, Mikulicz performed a radical operation (excision) in the case reported by Vollbrecht.[4] Von Winiwarter,[5] in 1899, also found it necessary to excise a sac that had refilled following treatment by puncture. To ensure drainage, Bickle[20] stitched the edges of the sac to the skin edges. Excision has come to be the accepted procedure for permanent relief. Tapping is frequently followed by recurrence within a few months and, infrequently, by infection, which creates a surgical emergency. Incision is followed by a long period of drainage and is often complicated by infection.

Although the operative technic of excision can be very easy, certain writers have reported difficulties. Coleman[28] found it advisable to use a scrotal and an abdominal incision. Lasbrey[22] believed the sac to be retroperitoneal, and he used two incisions; there was some difficulty in removing the sac. Curtis,[47] who experienced difficulty with a laparotomy incision, was nevertheless able to complete the operation through a groin incision. In the commoner properitoneal type, a groin incision should allow for an easy extraperitoneal removal of both the abdominal and scrotal portions of the sac. In some, the atrophied testis has been removed. The defect in the abdominal wall following excision of the hydrocele mass should be repaired by the approximation of the conjoined tendon to the inguinal ligament. Most operators leave a small drain in the scrotal cavity. In addition, a tight compression bandage over the lower abdomen and scrotum appears to be very advantageous in avoiding a large accumulation of serous fluid in the operative wound.

Case Report

L. R., a 25-year-old man, was admitted to the hospital because of a swollen scrotum. Swelling in the right scrotal region, which had first been noticed 8 years previously, had increased more rapidly during the preceding 2 years and had occasionally been painful. On admission, there was some abdominal swelling, but this caused no inconvenience.

The patient's general health was good. There were no serious illnesses or operations and no history of injury.

On physical examination, a visible mass causing deformity of the abdominal wall was evident in the right lower quadrant (Figs. 6 and 7). This mass, which was

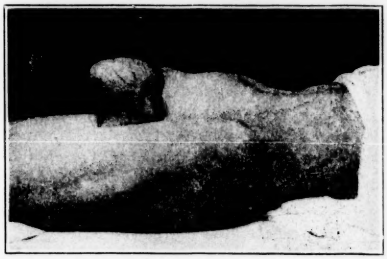

Figure 6. *Lateral View of a Patient with an Abdominoscrotal Hydrocele.*

smooth and firm, extended from above the level of the umbilicus to the scrotum, and from the region of the left rectus muscle well into the right flank. The abdominal mass seemed to be contiguous with a right scrotal swelling,

Figure 7. *Semilateral View of a Patient with an Abdominoscrotal Hydrocele.*

which had the typical consistence of fluid. The scrotal mass was easily transilluminated. Palpation of the scrotal mass caused a fluid wave in the abdominal portion. The swelling was not tender. There was a definite impulse on coughing. A tentative diagnosis of abdominoscrotal hydrocele was made.

On February 12, 1941, under spinal anesthesia, an oblique incision was made over the right lower quadrant and upper part of the scrotum (Fig. 8). The upper part of the incision included the fibers of the external oblique

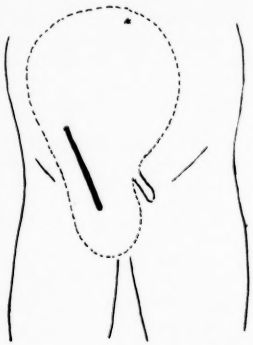

FIGURE 8. *Diagram of the Abdominoscrotal Hydrocele and the Incision Used for Removal.*

muscle and the conjoined tendons, and the lower part the usual layers of the scrotal wall. A good line of cleavage was found at the level of the enlarged cystic mass. The mass was easily enucleated by blunt and sharp dissection

FIGURE 9. *Photograph of the Excised Hydrocele Mass, Compared to a Large Lemon.*

and was removed by being slid out through the incision, the scrotal part being first delivered. An atrophied spermatic cord was clamped and bisected. The operation was accomplished without opening of the sac or the peritoneal cavity. The peritoneum was evident posterior to the hydrocele mass, but there was no evidence of any peritoneal reflection anterior to the mass. Fibers of the conjoined tendon and external oblique muscle were sutured to the inguinal ligament in an effort to support the lower abdominal wall. A small Penrose drain was left in the inguinal region, and one in the scrotal region. A firm

FIGURE 10. *Hydrocele Sac Opened and Emptied, with a Small Testis at the Lower End.*

compression bandage was applied to the lower abdominal and scrotal regions. Convalescence was uneventful.

The excised mass weighed 2600 gm. and contained 2000 cc. of olive-colored fluid (Figs. 9 and 10).

SUMMARY

The literature on abdominoscrotal hydrocele is reviewed, and the condition is described. A report of a typical case, with a discussion of the operative technic employed, is presented.

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THE USE OF DILANTIN SODIUM IN BRONCHIAL ASTHMA: A PRELIMINARY REPORT

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THE modern therapeutic armamentarium for the treatment of bronchial asthma is not satisfactory. Skin testing, with subsequent attempts to remove all suspected allergens, has not proved completely successful. The recent literature[1-5] has shown the importance of understanding the "asthmatic personality" and the role of psychogenic factors in bronchial asthma. The psychologic forces operating in this disease become more apparent when one is faced with the failures that occur under the present accepted medical regime. The search for a method of treatment that would exert its effect through nervous avenues and would be generally applicable led to the use of Dilantin Sodium in cases of bronchial asthma.

Sodium diphenyl-hydantoinate, commercially known as Dilantin Sodium, was described in 1937 and 1938 by Merritt and Putnam[6, 7] as a new anticonvulsant. The same authors[8] later reported excellent results with this drug in the treatment of epilepsy. Dilantin Sodium has, up to the present time, been applied solely in the treatment of epilepsy. The literature reporting its successful use in this condition has grown voluminous. Merritt and Putnam[9] report that "in addition to a relief or a great reduction in the frequency of the attacks, it was frequently noted by the parents of children that they were much better behaved, more amenable to discipline, and did better work in school." This improvement, they contend, must have been due in great part to the freedom from attacks, but they believe that the medication may also have produced other changes in the activity of the cerebral cortex. They continue with the statement that further study may conceivably lead to the use of Dilantin Sodium in conditions with similar cortical dysrhythmias other than those in the convulsive state.

After extensive use of Dilantin Sodium in epilepsy, Merritt and Putnam[9] discussed in detail the toxic effects, the great majority of which occur only when large doses are employed. The gastrointestinal symptoms of Dilantin Sodium intoxication were chiefly nausea and vomiting. Symptoms of toxic action of the drug on the central nervous system consisted of nervousness, tremor of the hands, drowsiness and headache, and ataxia. In 5 per cent of the patients, a toxic dermatitis varying from an erythema to a severe morbilliform rash appeared. Hypertrophy of the gums occurred, particularly in children and young adults. Those

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patients taking 0.3 gm. (4½ gr.) or less daily showed few or no toxic symptoms.

As discussed above, it was decided to employ Dilantin Sodium for the treatment of bronchial asthma in a selected series of cases. Only patients with repeated, frequent, acute attacks of asthma and a constantly "wheezy" respiration were included in the series. Every attempt was made to choose intractable cases of asthma that had not responded favorably to routine and accepted treatment. No case of purely seasonal asthma was included.

The ages of selected patients varied from three to fourteen years. The group included 4 boys and 3 girls, all of the white race. The sex factor was entirely coincidental.

All the patients treated in this experimental series had been skin tested. They were all found to be sensitive to many different foods as well as to many other irritants. Moreover, at different periods, all had had attacks of asthma severe enough to require subcutaneous adrenalin. Routine treatment of bronchial asthma had, in all these cases, been followed for varying lengths of time, with indifferent results. Such treatment had been given in each case for at least a year and in some cases much longer.

Dilantin Sodium was administered to the patients described below for periods varying from five months to one year. The first step before treatment was begun was the complete elimination of all other medication. Since the entire literature on Dilantin Sodium deals exclusively with its use in epilepsy, it was necessary to develop an arbitrary system of dosage for the treatment of bronchial asthma. The problem of controlling the administration of the drug in this series was solved by dispensing a week's supply to each patient at his or her weekly visit. This resulted in complete co-operation from the patients, as well as effective control of the doses taken. Each patient was first given 0.03 gm. (½ gr.) morning and night. Results were evaluated on the freedom from attacks and the absence of wheezing. If, after observation of one week under this dosage, symptoms still persisted, the patient was then given 0.03 gm. (½ gr.) three times a day. Dosage was increased by 0.03 gm. (½ gr.) daily at intervals of one week until the patient reported no attacks of asthma and no wheezing on moderate exertion. By this method of self-titration, it was found that 0.1 to 0.2 gm. (1½ to 3 gr.) daily was sufficient to keep the patients symptom free.

Each patient was advised to take part in all activities. No attempt was made to keep the children from entering situations and places that had previously precipitated attacks of bronchial asthma. In fact, as treatment with Dilantin Sodium progressed successfully, they were deliberately encouraged to enter such exciting and irritating environs as farms, moving pictures, fairs, circuses, parties and active games. Unrestricted diets were prescribed. Living quarters were not changed, and sleeping chambers were not specially prepared for the elimination of dust.

Case Reports

Case 1. E. K., a 5-year-old girl, an only child, with no family history of allergy, in infancy had severe eczema, which began to clear when she was about 2 years old. She was first seen at the age of 3 because of a persistent cough and wheeze following a tonsillectomy. On examination, a diagnosis of bronchial asthma was made. Subsequent attacks of asthma occurred at about weekly intervals. Routine skin testing showed positive reactions to many foods. No positive reactions were obtained when scratch tests were done with epidermals, grasses and weeds. The patient continued to have frequent attacks after the elimination of all known irritating factors; the medication consisted of ephedrine sulfate and allied drugs, which gave partial relief. Over a period extending from April, 1939, to July, 1940, she had twenty-four attacks of asthma severe enough to require injections of adrenalin in oil. All exciting play and activity had to be restricted because they apparently precipitated attacks. In July, 1940, the patient was first given Dilantin Sodium. After a few weeks of trial, the dosage was established as 0.1 gm. (1½ gr.) morning and night. No severe asthmatic attacks have occurred since that time, and she leads an active, normal life. There has been occasional wheezing respiration, but this occurs so infrequently and is so mild that no other medication is required and her normal activities are not interrupted. There has been no change in her environment since she was first seen. She resides in the same house, and her sleeping quarters are the same. She observes no dietary restrictions. Her general physical condition is good, and her appetite unimpaired.

Case 2. P. M., a 14-year-old girl, had a pronounced family history of asthma. Her father and her two brothers had bronchial asthma. The patient had eczema in infancy, which cleared. She was first seen in January, 1941, with an acute asthmatic attack. She had been having severe attacks about once each week for the previous 8 years. These attacks lasted 24 to 48 hours. For relief, she had been taking ephedrine capsules as well as inhaling some "powder" that her father used. Incomplete skin testing showed a marked allergy to many foods and a strong reaction to ragweed and goldenrod. The patient appeared poorly nourished and was found to be 14 pounds underweight. She was listless and disinterested in all activities. Her schoolwork was poor. Dilantin Sodium — 0.03 gm. (1½ gr.) morning and night — was ordered. With this dosage of the drug, she had many mild attacks. The dosage was slowly increased to 0.1 gm. (1½ gr.) morning and night. The symptoms then disappeared. The patient had been able to take active part in winter sports, and to skate, run and go out in cold and snowy weather — these activities had previously precipitated attacks. She has had several upper respiratory infections, but no subsequent asthma or wheezing. Her schoolwork has improved, and her parents describe her general mental attitude as "much brighter." There has been no restriction in diet

and no change in environment. Her appetite is excellent, and she has gained 8 pounds in weight.

CASE 3. M. M., a 9-year-old boy, was seen because of frequent "colds and cough" for the previous 5 years. At the age of 6, he had a tonsillectomy, with no relief. For the past 2 years, he had had attacks of bronchial asthma at intervals of about 2 weeks. No family history of allergy could be obtained. When first seen in December, 1940, the patient was having a severe asthmatic attack and had difficulty in walking up a few steps. His chest was fixed, and his breathing noisy and labored. Complete skin testing revealed sensitivity to many foods, as well as to dust, chicken feathers and ragweed. He was given Dilantin Sodium in doses of 0.03 gm. (½ gr.) morning and night. Wheezing continued until the dosage was increased to 0.03 gm. (½ gr.) thrice a day. With this dosage, all symptoms disappeared until March, 1941, when the patient had a severe upper respiratory infection, with some wheezing. Prompt relief was obtained by increasing the dose of Dilantin Sodium to 0.06 gm. (1 gr.) morning and night. There have been no attacks and no wheezing since that time. His general physical condition has improved, and he has gained about 7 pounds. He is now able to take part in all active sports, and his family reports a marked lessening of irritability. His school grades and attendance record for this year are excellent as compared with those of the previous year. There has been no opportunity to observe the effect of Dilantin Sodium on his seasonal allergy.

CASE 4. G. A., a 10-year-old boy with no family history of allergy, had two attacks of lobar pneumonia in 1935, at 4 years of age. On recovery, he began to have attacks of bronchial asthma. He was first seen in 1937, when he was 6 years old, and was referred to a Boston hospital for treatment. Skin tests at that time revealed sensitivity to many foods, as well as to ragweed and grasses. Since then, the patient had received various kinds of treatment, including osteopathic manipulation. Attacks occurred at about weekly intervals, but the patient was never completely free of symptoms. Because of his constant asthma, his activities were so restricted that he was practically an invalid. In December, 1940, he was given 0.03 gm. (½ gr.) Dilantin Sodium morning and night. It was necessary to increase the dosage rapidly to 0.1 gm. (1½ gr.) morning and night. Since the establishment of this dosage, the patient has had no attacks of bronchial asthma until the onset of his seasonal allergy. He has been able to take an active part in sports, and his schoolwork has shown marked improvement. He eats well and sleeps well. At present, he shows a gain of 8 pounds in weight. He is an entirely new personality, sparkling and lively. There has been no change in environment, and his diet is entirely unrestricted.

Since May, with the onset of this year's seasonal sensitivity to the grasses, he has had some wheezing and labored breathing, but no severe asthmatic attacks. Increasing the dose of Dilantin Sodium to 0.1 gm. (1½ gr.) thrice a day has had no appreciable effect. His present symptoms, however, are relatively mild and do not restrict his activities.

CASE 5. M. N., a six-year-old boy, had been seen at intervals since birth. Both his mother and father were allergic. From infancy, he had frequent attacks of spasmodic bronchitis, but otherwise his early history was essentially unremarkable. He had always been a high-strung, nervous boy — always a problem to control. He was pampered and markedly overprotected. In 1937, the patient had a severe case of pertussis. Convalescence was prolonged. Six months after recovery, he developed pneumonia. Recovery was again prolonged and was immediately followed by attacks of severe bronchial asthma. These attacks occurred at about weekly intervals. The patient was seen by an allergist, and skin tests showed a mild sensitivity to some foods. No grasses or weeds gave positive results. Even with elimination diets and complicated attempts to avoid contact with suspected irritating allergens, combined with the administrations of ephedrine sulfate and other standard treatment, he had little if any relief. Any new or exciting situation seemed to precipitate an attack. He was much restricted in his play by the parents and was absent from school a great deal.

In March, 1941, treatment with Dilantin Sodium was begun, following a severe asthmatic attack. The boy was first given 0.03 gm. (½ gr.) morning and night; this was found to be insufficient. In about 2 weeks, the dosage was increased to 0.03 gm. (½ gr.) in the morning and 0.1 gm. (1½ gr.) at night. He began to take part in social and physical activities, and his attendance record at school was excellent. Three upper respiratory infections with hyperpyrexia occurred, but did not, in contradistinction to the past record, result in attacks of bronchial asthma.

At the end of 2 months of treatment, the patient developed what his mother called an asthmatic attack. During this attack, his breathing was labored and he wheezed, but no rales could be heard in the chest. All these symptoms were pronounced when the patient was being examined or discussed, but disappeared when his attention was occupied. He has had four or five such episodes since, none of which required special treatment. It was believed that these attacks were not true asthmatic attacks, but there is much evidence that they were used as a device to attract attention. Because of the parents' extreme anxiety about the boy, however, he was referred to an allergist and an otolaryngologist for further checkup.

CASE 6. P. B. F., a 4-year-old boy with a family history of allergy — his paternal uncles and his father had severe hay fever — had an obstinate infantile eczema. At about 3 years of age, he developed frequent attacks of bronchial asthma. Skin tests showed marked positive reactions to many foods, as well as to the grasses and weeds. Asthmatic attacks occurred throughout the entire year at about weekly intervals. A tonsillectomy was done in November, 1940. Convalescence was uneventful, and the patient had no asthmatic attacks until March, 1941. With the resumption of attacks of bronchial asthma at that time, Dilantin Sodium treatment was begun. The initial dose was 0.03 gm. (½ gr.) morning and night. Some symptoms persisted until the patient was taking 0.1 gm. (1½ gr.) morning and night. At this dosage level, he was symptom free. Marked improvement was also noted in the residual eczema.

With the onset of his seasonal allergy, — caused by the grasses, — the patient's mother reported that he had moderate attacks of sneezing, morning and night. In an attempt to overcome these symptoms of vasomotor rhinitis, the dose of Dilantin Sodium was increased to 0.2 gm. (3 gr.) morning and night. This increase had little effect on the spasms of sneezing. One week after the patient began to take the 0.4 gm. (6 gr.) daily, he developed signs of central-nervous-system intoxication. He complained of dizziness, diplopia, nausea and vomiting, and a staggering gait was noticed. The drug was then discontinued for 5 days, during which he had several attacks of bronchial asthma. Dilantin Sodium was resumed in doses of 0.03 gm. (½ gr.) morning and night. Complete

relief from asthmatic symptoms was not obtained until he was given 0.1 gm. (1½ gr.) morning and night. His spasms of sneezing persisted.

This child was always markedly overprotected, and his activities greatly limited. His mother reported that he was always hyperactive, irritable and, in some respects, asocial. With the improvement in his asthmatic symptoms since taking Dilantin Sodium, he has been allowed more freedom of action and diet. At present, he is much more pleasant and amenable.

Case 7. D. R., a 3-year-old girl with no family history of allergy, had eczema, which had persisted since early infancy. In November, 1940, this patient — an only child — was seen with an attack of bronchial asthma. Her mother denied any previous attacks. These attacks recurred at frequent intervals. Skin tests revealed sensitivity to many foods, but no reaction to the grasses and weeds. In January, 1941, the patient was started on 0.03 gm. (½ gr.) Dilantin Sodium morning and night. At weekly intervals the dose was increased to 0.1 gm. (1½ gr.) morning and night. At this level, the patient remained free of any asthmatic attacks for months. The eczema also improved markedly.

In May, the child's mother failed to return for her supply of Dilantin Sodium, and the patient remained without treatment for a week. At the end of that time, she was again seen with a moderately severe attack of bronchial asthma. Dilantin Sodium, 0.1 gm. (1½ gr.) morning and night, was again given with complete cessation of symptoms. With this dosage, the patient has remained symptom free.

Summary

Because of recent work on the psychogenic aspect of bronchial asthma and the concept of the so-called "asthmatic personality," a search was made for a drug that would have a psychosomatic effect on children with bronchial asthma. Recent work with Dilantin Sodium and its application in the treatment of epilepsy have amply proved this to be a powerful and efficient anticonvulsant. The infrequency of toxic effects, in addition to its reported effect of improvement in the epileptic personality, marked the drug as one worthy of trial in cases of bronchial asthma.

Seven cases of intractable, severe bronchial asthma were selected for treatment with Dilantin Sodium. These cases were skin tested and were found to be sensitive to many different allergens. The ages of the patients ranged from three to fourteen years. The sex factor was not controlled, although in this series there were 4 boys and 3 girls. The patients received Dilantin Sodium for periods varying from five months to one year, although several were studied for a far greater length of time.

The dosage of Dilantin Sodium was determined for each patient by "self-titration" methods. When adequate dosage was maintained, 6 patients remained consistently free from attacks of bronchial asthma. Two patients reported abortive attacks, consisting of slight wheezing, which passed off rapidly. In only 1 case did toxic symptoms result from the ingestion of the drug. In this case, the toxic symptoms cleared rapidly on withdrawal of the drug, and the patient was able to resume treatment with a slightly smaller dose.

In 2 cases complicated by seasonal allergies, nasal and ocular symptoms of the allergy occurred and could not be controlled with Dilantin Sodium.

During the administration of the drug, there were no change in environment and no dietary restriction. During this period, some of the patients suffered acute upper respiratory infections, with no resulting bronchial asthma, in sharp contrast with the previous history of these patients. To test the efficacy of Dilantin Sodium in controlling asthmatic attacks brought on by emotional upsets, many patients were encouraged to enter situations and environments that formerly precipitated attacks of bronchial asthma. With this drug as the sole medication, the patients were consistently free of attacks of bronchial asthma, and they were able to engage normally in athletic and social activities. In the 1 case in this series in which complete success was not obtained, the lack of parental co-operation and understanding was an important factor.

Cases 2, 3 and 4 were marked by a distinct change in personality, with lessening of irritability. The patients were reported to be much brighter mentally and much easier to live with. In Case 2, a distinct improvement in schoolwork was noted.

In 2 cases, a stubborn eczema, which had persisted since infancy, cleared to a remarkable degree while the patients were taking Dilantin Sodium.

Conclusions

Dilantin Sodium gave marked relief in 6 of 7 cases of bronchial asthma.

The drug must be given continuously to prevent the attacks.

The modus operandi of this drug in cases of bronchial asthma cannot be determined from the results with this small group of patients.

Personality changes were observed in these patients.

Concomitant eczema improved with the administration of Dilantin Sodium in 2 cases.

A new field of investigation, which requires much more clinical and laboratory work with Dilantin Sodium in bronchial asthma, is open.

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CLINICAL NOTE

THE ASSOCIATION OF PRIMARY NEOPLASM OF THE LIVER WITH HEMOCHROMATOSIS*

Report of a Case

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IT IS widely recognized that the severer grades of diffuse hepatic cirrhosis are frequently complicated by a primary hepatic neoplasm. Counseller and McIndoe[1] reported 5 such cases in 127 cases of portal cirrhosis, an incidence of 3.9 per cent. Stewart[2] collected 9 cases in 120 cases of well-marked cirrhosis, an incidence of 7.3 per cent. The first authors even suggest that primary carcinoma of the liver develops in 3 to 4 per cent of patients with cirrhosis.

This type of neoplasm also occurs in association with another type of cirrhosis, namely hemochromatosis. In this disease, the fibrosis is believed to result from the reaction to a diffuse deposit of hemosiderin throughout the liver and other organs. Sheldon,[3] in his excellent monograph on hemochromatosis, published in 1935, collected from the literature 345 cases in which 20 patients had primary cancer of the liver, an incidence of 5.8 per cent. This is in agreement with the figures for cirrhosis in general.

The following case of hemochromatosis is reported as an example of this interesting association with hepatoma.

Case Report

G. M. (P. B. B. H. Medical 59247), a 62-year-old married man, entered the medical service of the hospital on March 16, 1941, with the complaint of weakness. For several years, he had noticed gradually increasing pigmentation of his skin, without other symptoms. Three months before entry, he noticed a rather sudden onset of weakness, anorexia, polydipsia and polyuria, and was found to have glycosuria by his local physician. He was regulated satisfactorily by dietary management with 22 units of protamine insulin and 30 units of regular insulin every morning. Two weeks prior to entry, the patient noticed marked weakness in his left arm and leg and soon became unable to raise his left hand.

The family history was noncontributory. He had enjoyed excellent health until his present illness. He did not use alcohol, and he had not been exposed to any occupational hazard.

Examination showed a well-developed, moderately obese and chronically ill elderly man. The skin was generally pigmented brown, most markedly on the forearms and abdomen. There was slight pigmentation of the oral mucous membranes and at the angles of the lips. Body and axillary hair was scant, and the pubic hair was of the female configuration. The blood pressure was 96/50; 6 weeks previously, it had been 140/70. The heart was not enlarged, the rate and rhythm were normal, the sounds were distant, and no murmurs were heard. The lungs were clear. The liver edge was felt 4 cm. below the right costal margin and was smooth and firm. There was no free fluid in the abdomen. The cranial nerves were intact, but there was marked weakness of the left arm and leg. Sensation was unimpaired. The tendon reflexes were slightly diminished on the left side. There was no Babinski sign on either side.

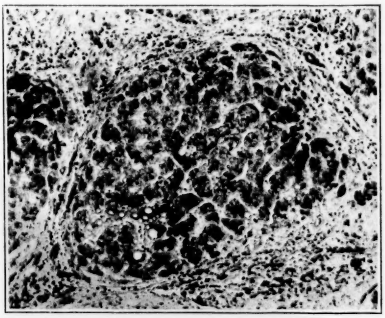

Figure 1. *Photograph of a Section of the Liver, Showing Fibrosis and the Deposition of Hemosiderin.*

The blood Hinton reaction was negative. Examination of the blood showed a red-cell count of 4,590,000 with a hemoglobin of 100 per cent (Sahli), and a white-cell count of 10,000. Urine analysis showed a ++++ test for sugar, but no acetone. Blood chemical findings were a nonprotein nitrogen of 27 mg., a sugar of 218 mg., a cholesterol of 170 mg. and a serum protein of 7.5 gm. per 100 cc., with an albumin of 3.7 gm. and a globulin of 3.8 gm. per 100 cc. The carbon dioxide combining power was 20 milliequiv. per liter, the sodium 127 milliequiv. per liter, the icteric index 17, and the sedimentation rate 5 mm. per hour. A bromsulfalein liver-function test showed 90 per cent retention in 30 minutes. The vital

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capacity was 1700 cc. The basal metabolic rate was −2 per cent. An electrocardiogram showed low voltage, premature auricular beats and a very small R wave in Lead 4F.

The clinical course was afebrile except on one occasion, when there was a rise in temperature to 101°F. Because of the symptoms of weakness and nausea and the findings

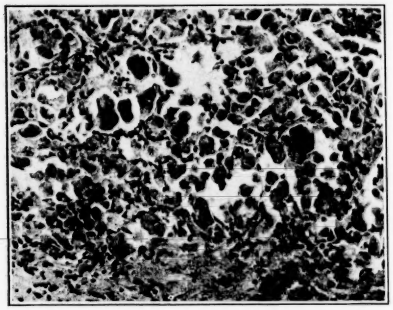

FIGURE 2. *Photograph of a Section of the Hepatoma.*

of low blood pressure, pigmentation of the oral mucous membranes and low blood sodium, the possibility of a concurrent adrenal insufficiency was considered. Accord-

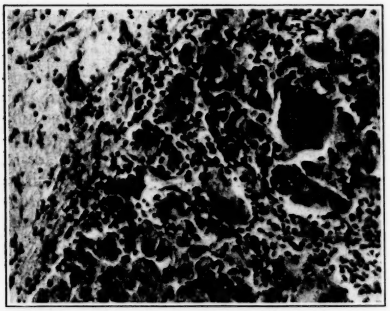

FIGURE 3. *Photograph of a Section of a Metastasis in the Adrenal Gland.*

ingly, sodium chloride was added to the diet, and 20 mg. per day of desoxycorticosterone acetate was administered intramuscularly. The patient became weaker, and neither the blood pressure nor the blood sodium rose. Despite 50 units of regular insulin daily, the blood sugar rose to 450 mg. per 100 cc. Cheyne–Stokes respirations became apparent, and the venous pressure increased to the equivalent of 240 mm. of water. The patient was rapidly digitalized. On the 6th hospital day, acute pulmonary edema developed, and the patient expired while a phlebotomy was being attempted.

Autopsy. The principal findings at autopsy consisted in hemochromatosis, with marked atrophy and fibrosis of the pancreas, cirrhosis of the liver and malignant hepatoma (Fig. 1). The last had metastasized to the lymph nodes at the hepatic hilus and to the right cerebral hemisphere (Fig. 2). No lung metastases were seen. Pigment deposits consisting predominantly of hemosiderin and to a lesser extent of hemofuscin were present in all organs. They were most abundant in the pancreas, liver and lymph nodes. The heart and particularly the parathyroid, thyroid and pituitary glands, epididymis and choroid plexus represented other sites of marked pigmentation. The adrenal glands displayed a fair degree of pigmentation (Fig. 3) but were not otherwise histologically unusual. The heart weighed 380 gm., the liver 2560 gm., and the pancreas 160 gm. The tumor in the liver measured 4 by 5 by 7 cm., and the metastatic nodule in the brain was 1.1 cm. in diameter (Fig. 4).

Inasmuch as the presence of the hepatoma was unsuspected clinically in this case, the discovery that the cerebral metastases accounted for the hemiplegic symptoms was doubly surprising. Involvement of the brain by metastasis from a liver-

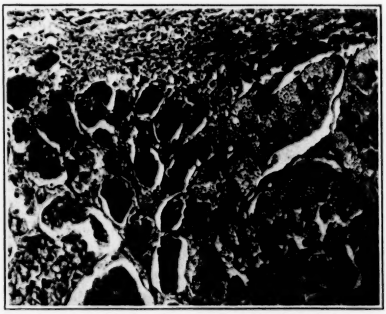

FIGURE 4. *Photograph of a Section of a Metastasis in the Brain.*

cell carcinoma is unusual. Of 33 cases of hepatoma with ordinary cirrhosis and 17 with hemochromatosis reported by Stewart,[2] none had secondary involvement of the brain by the tumor.

Adrenal insufficiency was suggested clinically by asthenia, nausea, low blood pressure, low blood sodium and pigmentation of the oral mucous membranes, in addition to the pigmentation of the skin. Lack of response to salt and desoxycorticosterone therapy, however, as well as the only slightly altered histologic appearance of the adrenal glands at autopsy, made this uncertain. The role of other endocrine-gland changes in the production of symptoms in this disease has led to speculation. Butt and Wilder[4] suggest that impotence and atrophy of the hair and skin may be due to a deposition of hemosiderin in the anterior lobe of the hypophysis. To explain the pigmenta-

tion of the oral mucous membranes, these authors suggest a deposit of melanin secondary to the involvement of the adrenal gland by hemosiderin. These hormonal interrelations are of interest but are difficult to analyze.

Summary

A case of hemochromatosis is reported in which a primary hepatoma with metastasis to the brain occurred. The relation of hepatoma to hemochromatosis is discussed. Some of the clinical features of this case could be attributed to adrenal insufficiency.

I am indebted to Dr. Orville T. Bailey for the photographs used in this report.

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MEDICAL PROGRESS

TOXIC REACTIONS FOLLOWING SULFONAMIDE TREATMENT*

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BOSTON

THAT toxic reactions follow the use of the various sulfonamides is well known. That they vary in their frequency and severity, as well as in their clinical features, is also well recognized. The purpose of this report is to summarize the various toxic reactions as they are observed in patients following sulfonamide treatment, and to discuss their significance.

For purposes of discussion, the toxic reactions can be divided into several groups in accordance with the system involved and the time of their occurrence (Fig. 1). Toxic reactions referable to the gastrointestinal tract, the hematopoietic and the renal systems are the most important and frequent. The time of their occurrence may be divided into the prompt, the accelerated and the delayed reactions. Although there is very little information available concerning the precise mechanism of the production of side effects, it seems clear that some of the reactions are due to the direct toxic effect of the drugs on tissues, whereas others are due to hypersensitive reactions that are similar in many respects to drug hypersensitivity in general.

Skin Reactions

Among the common untoward reactions to the sulfonamides are various skin eruptions. They are characterized by their pleomorphism, and are frequently accompanied by other signs of drug intoxication or hypersensitivity. They vary in frequency with different drugs (Table 1), and they are often widespread in distribution. The lesions cannot be inhibited by the administration of para-aminobenzoic acid. There is nothing distinctive about the eruptions, since they may be erythematous, morbilliform, urticarial or purpuric, and in some cases a generalized exfoliative dermatitis, with massive edema, appears. Lesions resembling erythema nodosum are most frequently seen following sulfathiazole therapy. One of the curious features of some of the cases of dermatitis, especially those following sulfanilamide, is the fact that the eruption develops after exposure to sunlight or, at least, is made worse following such exposure.

The skin eruptions occur at one of three periods following the administration of the drugs. The usual time is between seven and nine days after the drug is started, although the lesions may appear as early as the fourth day or as late as the fourteenth day (delayed reaction). They may occur, however, as a prompt or accelerated reaction within twenty-four hours after the drug has been started, or as late as two to six weeks. When the skin eruptions are prompt or accelerated, they almost invariably occur in persons who have previously received the same or a closely related drug. For example, the usual story is that they received the same or a different sulfonamide at some time in the past, and that a reaction consequently followed within seven to fourteen days. This delayed reaction, which was self-limited in duration, disappeared following withdrawal of the drug. Then,

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after an interval varying from a few days to months or even several years, the same drug or a different one is given, with a prompt reaction. The prompt reactions may occur after single small doses, and they may be more extensive and serious than the previous reactions, since they are sometimes associated with exfoliative dermatitis or the signs of toxic hepatitis. Although these prompt or accelerated reactions occur oftenest in patients who have had reactions following the first experience with the drug, they may appear in those who have previously had the drug without any noticeable reactions. Patients who have acquired sensitivity to sulfapyridine may react in a similar manner to sulfamethylthiazole or sulfapyridine but not to sulfanilamide, and patients who are sensitive to the esters of para-aminobenzoic acid (procaine hydrochloride) may be sensitive to sulfanilamide (para-aminobenzoic sulfonamide). It is plain, then, that the hypersensitivity to the drug may be specific, and that the reactions may follow the exhibition of a closely related drug. This

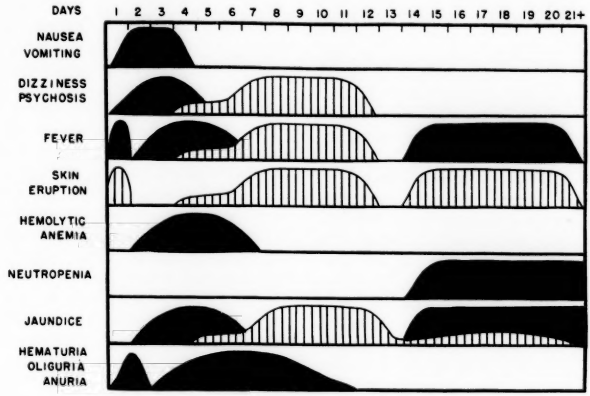

FIGURE 1. *Chart Showing the Time of Appearance of the Various Toxic Manifestations of the Sulfonamides.*

The vertically hatched areas represent skin eruptions; they are superimposed on the lines indicating other toxic manifestations to demonstrate the possible coexistence of complications.

TABLE 1. *Frequency of Toxic Reactions Following Various Sulfonamides.*

Toxic Reaction	Sulfanilamide	Sulfapyridine	Sulfathiazole	Sulfaguanidine	Sulfadiazine
Nausea or vomiting, or both	10–20%	40–55%	23–40%	2–5%	5–9%
Mental disturbances, including toxic psychoses	0.5–1%	0.3–5%	0–2%	0	0
Skin eruption	2–5%	4–5%	8–10%	Occasional	2–3%
Fever	10%	2–5%	5–6%	Occasional	1%
Anemia	1–2%	2–3%	Very rare	Not reported	Not reported
Leukopenia	0.1%	0.1–0.5%	Rare	Not reported	2%
Hematuria	0	2–3%	2–3%	Not reported	0.5–1%
Oliguria	0	0.1–0.5%	0.5–1%	Not reported	0.5–1%
Anuria, with nitrogen retention	0	Not reported	0.5–1%	Not reported	0.5–1%
Jaundice	Rare	Not reported	Rare	Not reported	Not reported
Hepatitis	Rare	Not reported	Rare	Not reported	Not reported
Purpura hemorrhagica	Rare	Rare	Not reported	Not reported	Not reported
Gastrointestinal bleeding	Occasional	Occasional	Not reported	Not reported	Not reported
Stomatitis	Rare	Rare	Not reported	Not reported	Not reported

suggests that there is a common substance in the various drugs to which some patients become sensitive.

In most cases, the prompt hypersensitive skin eruptions are accompanied by fever, and in some, they may be associated with such features as toxic hepatitis.

Delayed skin eruptions, which were first described by Hageman and Blake, occur commonly between the seventh and the ninth day after the drug is started, and fever is associated with the eruption in about half the cases. The fever may subside within two to seven days after the drug is withdrawn, but the skin eruptions may persist for several weeks or even longer. Other associated features are generalized edema, enlargement of the lymph nodes, leukocytosis (often reaching a count of 70,000 or 80,000), transient jaundice without anemia, and eosinophilia (20 to 55 per cent). The delayed skin eruptions may also be a feature in the patients with neutropenia or in the cases of jaundice occurring as late as the sixth week after the drug has been discontinued.

Fever

Febrile reactions following the sulfonamides may be prompt, accelerated or delayed. They may occur alone, with a skin eruption, or with other manifestations of drug intoxication or hypersensitivity. They may be superimposed on the fever of infection, or they may appear after the fever of infection has disappeared. In a few cases, they occur several days after the drug has been discontinued. These episodes are usually self-limited and last from two to nine days, the usual duration being two to four days. They occur with varying frequency following the different sulfonamides and are commonest after sulfathiazole and least common following sulfadiazine (Table 1).

Patients who develop febrile reactions within the first twenty-four hours have almost invariably received the drug previously, with or without signs of intoxication. When the fever develops or is increased within two to six days following its exhibition, there is generally an associated hemolytic anemia.

Prompt febrile reactions following a single dose of the sulfonamides may be an isolated feature, or they may be followed or accompanied by a skin eruption, toxic hepatitis, leukopenia or hemolytic jaundice.

The onset of the fever may be very abrupt and accompanied by a chill and a skin eruption. Such reactions usually follow the repeated use of the same or a related drug, although a patient may be sensitive to one and not to another. Dowling has reported that a patient who reacted to a second dose of sulfadiazine failed to react to sulfathiazole, sulfapyridine or sulfanilamide. Davidson and Bullowa reported a case in which fever and a skin eruption followed the use of sulfapyridine or sulfamethylthiazole in a patient with acquired sensitivity to sulfapyridine; the same patient, however, failed to react to sulfanilamide.

Renal Complications

Three renal complications may follow the use of the sulfonamides: hematuria, renal colic, and oliguria or anuria. They have been described following sulfapyridine, sulfathiazole and sulfadiazine, but not after sulfanilamide (Table 1). To understand these phenomena, one must be familiar with the facts concerning the excretion of the free and combined or acetylated sulfonamides by the kidney. It is now firmly established that, once the various sulfonamides are absorbed from the gastrointestinal tract, a part of the drug remains free and the remainder is changed by the process of acetylation to the combined form, and both fractions are excreted almost quantitatively by the kidney. The acetylated drugs are more insoluble than the nonacetylated, so that when the urine is concentrated by reabsorption of water by the kidney tubules the precipitation of the acetylated compounds is likelier to occur than that of the free compounds. The crystals may form in the tubules or the pelvis of the kidney, or they may precipitate out in the ureters or the bladder; in either event, they cause obstruction to the free flow of urine, and oliguria or anuria may follow. This may be preceded by attacks of renal colic or hematuria, or both. The hematuria is not always associated with renal colic, and may occur without any of the signs of obstruction. In these cases, it is difficult to escape the conclusion that there has been actual irritation of the glomeruli. When there is oliguria or anuria, the nonprotein nitrogen of the blood increases, and signs of renal insufficiency and even uremia may follow. It is rare indeed for any patient who has shown symptoms and signs of renal insufficiency during sulfonamide therapy to continue to show them following the discontinuation of treatment, unless the kidneys have been insufficient prior to the drug treatment. In other words, if permanent renal damage ever occurs from sulfonamide treatment, it must be exceedingly rare.

From what has been said, it is apparent that the concentration of the urine, the duration of treatment and the functional capacity of the kidney prior to administration of the drug are all impor-

tant considerations in the renal complications of sulfonamide therapy.

Hematuria, which is the commonest manifestation of renal irritation, may occur as an isolated feature or in association with renal colic. It is more frequently seen after sulfapyridine than after sulfathiazole or sulfadiazine, probably owing to the variation in the amount of drug acetylated before it is excreted by the kidney. Hematuria may occur as early as the first day of treatment in patients receiving intravenous therapy, but, as a rule, it is seen on the second and third days, or later. In several reported cases, renal colic and hematuria appeared several days after the drug had been discontinued, probably because the fluid excretion was decreased before all the drug had been eliminated from the body. Generally speaking, hematuria disappears following discontinuation of the drug and the forcing of fluids to 2500 cc. daily.

When the fluid intake is inadequate because of vomiting, stupor or the intoxication accompanying the infection, or when renal insufficiency precedes the use of the drugs, oliguria and even anuria may occur. When the sodium salts are given intravenously, hematuria and oliguria may be seen within twenty-four to forty-eight hours. In most cases, however, oliguria is first noticeable after the drug has been given for several days. It is for this reason that the fluid intake and urinary output should be watched carefully so long as the drug is being given. Nitrogen retention accompanies the oliguria, and in many cases, the symptoms and signs of uremia develop. If any of these signs appear, the drug should be discontinued at once, the fluid intake increased to at least 3000 cc. a day, and cystoscopy carried out to ascertain whether there is an obstruction of the ureters. Aside from agranulocytosis, the renal complications are the most serious and require prompt action if they occur during the course of the treatment.

Jaundice

Following the use of the sulfonamides, particularly sulfanilamide, jaundice is occasionally encountered, owing to the development of a hemolytic anemia or a toxic hepatitis. Associated with the jaundice, there may be an exfoliative dermatitis, other skin eruptions or neutropenia. The time of the appearance of the jaundice is significant. It may be accelerated or delayed. During the first week of treatment, icterus usually signifies a hemolytic anemia.

When delayed, the jaundice may appear between the eighth and the fourteenth day, or even later. It is accompanied in most cases by exfoliative dermatitis — occasionally, by neutropenia. One case has been reported by Garvin in which jaundice and exfoliative dermatitis were observed six weeks after the drug had been discontinued.

In the cases associated with the signs of hemolytic anemia, the jaundice is due to increased blood destruction as well as to toxic hepatitis, since bilirubin appears in the urine and the bromsulfalein test usually shows retention of dye. Watson and Spink have demonstrated impaired liver function following the administration of sulfanilamide.

When jaundice without anemia occurs within a few days after the drug is started, this usually means that the patient has been sensitized to the drug by a previous experience with it. As a rule, there was some sign of intoxication during the first course of treatment, but the signs of intoxication may have been absent. It is well to remember, as previously mentioned, that sensitization may occur without causing symptoms or signs at the time, the only evidence of sensitization appearing after the second exhibition of the drug at a later date. Cases have been observed in which jaundice followed a small amount of the drug, and was preceded by a chill, high fever and a skin eruption. Patients who have previously shown signs of hypersensitivity should never be given the drug a second time.

Enlargement of the liver and spleen and, in occasional cases, ascites accompany the jaundice. In most of the reported cases of toxic hepatitis, the prognosis is favorable, although it is poor when exfoliative dermatitis or neutropenia is also present.

Anemia

Anemia following the sulfonamides is of two types: acute hemolytic and slowly progressive. It is most frequent after sulfanilamide, but it may occur after any of the drugs (Table 1). Harvey and Janeway were the first to report acute hemolytic anemia following sulfanilamide, and since then it has been observed with varying frequency in different clinics. Wood states that 2.4 per cent of adults and 8.3 per cent of children developed acute hemolytic anemia following sulfanilamide. This is the highest recorded incidence of this complication, but it serves to stress its importance.

Briefly, the course of the acute hemolytic anemia is as follows. Within one to seven days after sulfanilamide is started, the patient begins to complain of nausea and dizziness. There is commonly an exacerbation or an onset of fever. Within a short time, the patient becomes pale and sometimes icteric because of the rapid destruction of blood. The blood shows an anemia, with leuko-

cytosis; there are urobilinogenuria, bilirubinemia and, in some cases, hemoglobinemia and hemoglobinuria. Following the discontinuance of the drug, the forcing of fluids, and blood transfusions, recovery occurs in most cases, although the anemia may persist for as long as two to four weeks.

The leukocytosis may be very high with a leukemoid reaction; that is, the white-cell count may be well above 100,000, and nucleated red blood cells and myelocytes may be present in increased numbers.

From the studies of Watson and Spink, as well as those of Ham and of Antopol, Goldman and Sampson, it is now evident that profound changes occur in the hemoglobin metabolism and in the red blood cells of patients receiving sulfanilamide. Evidence of increased blood destruction and changes in the fragility to varying concentrations of salt solutions has been obtained, and suggests that sulfanilamide in some mysterious way makes the red blood cells vulnerable to rapid destruction. At the same time, it has a profound effect in the bone marrow, causing the changes that are responsible for the hyperleukocytosis with leukemoid reaction.

Of great significance is the observation that a recurrence of the anemia may follow the second course of the drug.

The second type of anemia, namely, the slowly progressive form, is exceedingly common in patients who receive large amounts of the sulfonamides for two weeks or longer. This type is difficult to interpret, since the infections that are being treated are often contributory. There seems to be no doubt that the anemia in many of these cases is due to the sulfonamides, since it occurs in patients with infections, such as gonococcal arthritis, that in themselves do not produce anemia. Some of these patients show splenomegaly. In any case, therefore, it is well to remember that a slowly progressive anemia is common following sulfonamide treatment, and that adequate means should be taken to recognize and treat it.

Neutropenia and Agranulocytosis

A decrease in the total leukocyte count below 5000, with or without a corresponding decrease in the granulocytic cells, is not too uncommon following sulfonamide treatment. It is most frequently observed following sulfanilamide, and less often following sulfapyridine and sulfathiazole (Table 1). Although leukopenia is not infrequent after sulfadiazine, agranulocytosis must be rare, since, so far as I can determine, it has not been reported.

When agranulocytosis appears, it is a most serious complication: about 70 per cent of patients die. The usual time of its occurrence is between the fourteenth and the twenty-first day after the drug has been started, and it is most frequent in patients who have received a large amount of the drug continuously for that length of time. Occasionally, agranulocytosis is observed as early as the sixth or as late as the thirty-fifth day. In a few cases, it appears within a few days to two weeks after the drug has been discontinued. Once leukopenia occurs and the patient recovers, neutropenia and fever frequently develop following the second attempt to resume treatment. This was a feature of the case described by Jones and Miller.

The onset of agranulocytosis is usually accompanied by fever, sore throat, ulcerative stomatitis and pharyngitis, and a skin eruption. In a few patients, jaundice develops. Other signs of drug intoxication often precede the onset of agranulocytosis, such as skin eruptions, fever, anemia, jaundice and leukopenia. When these features appear, treatment should immediately cease.

The course of agranulocytosis is usually rapidly fatal in at least 70 per cent of all cases, and death occurs between four and six days following the onset of symptoms. The treatment consists in stopping the drug, the use of Pentnucleotide and blood transfusions, and the local treatment of the throat infection. This subject has been adequately reviewed in a recent progress report by Jackson.

Miscellaneous and Infrequent Signs of Intoxication

Ocular Lesions

The following affections of the eyes have been observed: conjunctivitis and scleritis, acute myopia, optic neuritis and yellow vision. Conjunctivitis and scleritis are encountered following sulfathiazole. Acute myopia has followed sulfapyridine, with edema of the lens. Temporary optic neuritis has been described after sulfanilamide, and yellow vision was complained of by one of Dowling's patients following sulfadiazine. All these disturbances are temporary and subside when the drug is withdrawn.

Symptoms Referable to the Central Nervous System

Psychoses. Irritability, drowsiness and stupor, with mental depression, disorientation as to time and place, and hallucinations, are not infrequently encountered during treatment with the sulfonamides, and disappear rapidly once the drug is discontinued. The relative effect of the infection itself

and of the drug in causing the mental symptoms is sometimes difficult to assess, since many patients with pneumonia or other febrile illnesses ordinarily develop delirium or other signs of mental disturbance during their infections. There is no doubt, however, that the sulfonamides contribute to the production of temporary mental disturbances in some cases, since their withdrawal is followed by the disappearance of these symptoms.

Polyneuritis. A rare complication of sulfonamide treatment is polyneuritis, especially after sulfanilamide or sulfathiazole. In most of the reported cases, the drug was given in large amounts over a period of several weeks. The prognosis is usually good, although at least several months may be required for the patient to recover.

Thrombopenic Purpura Hemorrhagica

This is a rare complication of sulfanilamide or sulfapyridine intoxication, and one that should call for immediate discontinuation of the drug. On the whole, the prognosis is good following withdrawal of the drug.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28071

PRESENTATION OF CASE

A forty-five-year-old housewife was admitted to the hospital because of profuse vaginal bleeding of eight hours' duration, following a long course of menstrual irregularity.

Following the menarche, at twelve years, the menses were quite profuse. At the age of twenty-one, the patient received three radium treatments in another hospital, following which the menses stopped for six weeks. At the age of about thirty, a "tube and ovary" were removed at the other hospital, and another course of radium therapy was given. In the seven years following this, the menses were absent, and the patient experienced hot flashes. The menses then returned, and were regular, although scanty. Following the last regular period, one year before entry, there was amenorrhea lasting seven months. There was then slight, continuous bleeding for two months, stopping two days before entry. Following a strenuous evening, the patient was aroused early in the morning by profuse vaginal bleeding, with the passage of large clots. Throughout the course of the illness, there were no other symptoms until the last episode of vigorous bleeding, when there was some cramping. The patient had been married for seven years but had never been pregnant.

The family history was irrelevant. Appendectomy and cholecystectomy had been performed some years previously.

On admission, the patient appeared well developed and nourished. The chest and upper abdomen were normal. There was moderate suprapubic tenderness, with slight resistance to palpation. There was some suggestion of a pelvic mass. However, deep palpation and vaginal examination were omitted because of the recent bleeding. Four well-healed scars of previous abdominal operations were present.

The temperature was 100°F., the pulse 100, and the respirations 20. The blood pressure was 120 systolic, 90 diastolic.

Examination of the blood showed a red-cell count of 4,730,000 with 14.3 gm. hemoglobin. The blood Hinton reaction was negative. The urine was normal.

On the fifth hospital day, an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. MARSHALL K. BARTLETT: When we look over the history, there are several interesting points and several things that we should like to know. I assume that the periods from the age of twelve up to twenty-one, although profuse, were regular. There is no such statement, but irregularity is a point significant enough to have been mentioned if present.

The next interesting thing is that the patient was given three radium treatments at the age of twenty-one, — in other words, twenty-four years previous to entry, — following which she had no periods for six weeks; then, at about thirty, or fifteen years before entry, she had a tube and an ovary removed and another course of radium. This was followed by a longer period of amenorrhea, lasting seven months, during which she had hot flashes. Then, the menstrual periods returned, being regular although scanty until a year before entry, when they stopped. It would be interesting to know whether the patient had hot flashes during the time she was having those periods and during the last period of amenorrhea; the arithmetic does not come out right, to my way of thinking. She is said to have had the last period one year before entry, but amenorrhea for seven months and flowing for two months, stopping two days before entry, add up to only nine months. That is a minor point, but if one wanted to consider the possibility of pregnancy, the slight difference might be important. It is interesting that the last flow was continuous, whereas previously she had always had regular cycles.

What are the possible causes for this? I think that even on the basis of this meager physical examination it is possible to rule out a full-term pregnancy, and from the dates it would have to be full term. Was this a dysfunctional type of flow associated with endocrine imbalance? Certainly, there is a good background, with all the menstrual difficulty that is reported. Could the bleeding have been due to a polyp of the cervix or one of the endometrium? I think that the profuse bleeding just before entry would be unusual for cervical polyp, although possible, and that it could be associated with an endometrial polyp.

Could it be associated with the presence of fibroids? It could, and I see no way to rule it out on the basis of this information. The same thing applies to a benign ovarian cyst, if one was present. I do not see how one can be sure. Of these benign conditions, it seems to me that the

most probable one is the dysfunctional type of flow based on endocrine imbalance.

What could we say in favor of a malignant cause? Two points rather favor that. In the first place, the patient had had two courses of radium treatment a number of years before entry, which raises at least a theoretical possibility that she might have developed a malignant neoplasm on the basis of previous radiation. The other thing is the bleeding, which was different in type from what she had had before. It was continuous rather than intermittent. Could this have come from a carcinoma of the cervix? I believe that it could. Certainly, a carcinoma of the cervix can occasionally cause a sudden profuse hemorrhage. It is not common, but we do see it. Could it have been a carcinoma of the endometrium? I should think that it could, and if we give any weight to the previous radiation, the endometrium would be the logical place to look for it. The fact that the patient had cramps with the last episode that brought her to the hospital suggests something inside the uterus. How about a malignant ovarian cyst? Certainly, that can give slight continuous bleeding for two months. I think it would be unlikely to give profuse hemorrhage such as she had just before she came in. Could it have been a carcinoma of the tube? We know that that gives slight bleeding, with intermittent gushes, but I do not believe it would give a profuse type of hemorrhage.

We have all these possibilities, and I do not see that we have very much to go on in choosing between them. The points we have to work on are fairly small ones, but we must make a choice. It seems to me an even choice between a benign type of dysfunctional bleeding and bleeding on a malignant basis. Of the two, I am a little inclined to think that it was probably on a malignant basis, and of the various possible sites of carcinoma, the endometrium is probably the most logical choice.

Dr. Jacob Lerman: Could the patient have been radiated because they found a malignant ovary or something else at the time? Why was she given radium?

Dr. Bartlett: I should think that she was given small doses of radium to control the bleeding. If the ovary had proved to be malignant, it would have been more reasonable to go back and do a hysterectomy, with removal of the other tube and ovary as well.

Clinical Diagnoses

Functional uterine bleeding.
Endometrial polyp.

Dr. Bartlett's Diagnosis

Carcinoma of endometrium.

Anatomical Diagnosis

Carcinoma of endometrium.

Pathological Discussion

Dr. Tracy B. Mallory: The patient was examined vaginally under anesthesia. A normal cervix was found. The uterus was curetted, and a considerable amount of polypoid material, which grossly did not look malignant, was removed, but a frozen section showed that it was carcinoma. The curettage was then followed up by a complete hysterectomy, and a carcinoma of the fundus was found of quite undifferentiated character and a rather high degree of malignancy.

Dr. Langdon S. Parsons: How much did the uterine radiation have to do with this?

Dr. Mallory: There is no way of telling. The one remaining ovary showed a single cyst, but was otherwise negative. The uterus was still quite small. There was no obvious extension of the tumor into the pelvis. It was not possible to feel the liver for metastases, because of adhesions of the omentum secondary to the previous operations, but at the end of the operation it seemed that a favorable result might be expected.

CASE 28072

Presentation of Case

First admission. A forty-seven-year-old plumber was admitted to the hospital complaining of steady abdominal pain of twenty hours' duration.

The patient was fairly well until two years before admission, when he first noticed a steady, aching, low substernal pain and feeling of compression, which had persisted almost constantly since that time. The discomfort was usually worse at night and was sometimes relieved if the patient walked the floor. It was never severe enough to keep him awake, and was not influenced by exertion, breathing or swallowing. At approximately the same time, he began having dull headaches, became weak and tired, and developed nocturia (once). He entered an outside hospital for a checkup, and was told that his blood pressure was "276." After discharge, he continued to work, and was fairly well until twenty hours before admission, when while eating a sandwich and drinking coffee at 10 p.m., he was suddenly seized with a severe steady pain beneath the xiphoid; this soon radiated through to the back and up between the shoulder blades. He felt nauseated and vomited

a small amount of food. The pain increased in severity, and half an hour after its onset he attempted to "walk it off." He then experienced a severe cramp in the back of the right leg, which remained until he stopped walking. It failed to return, thereafter, but the subxiphoid epigastric pain continued in spite of two hypodermic injections given by his physician. He finally fell asleep about 4 a.m., but was awakened at 7 a.m. by the same pain. Throughout the morning and afternoon before admission, the pain continued while he restlessly paced the floor.

Physical examination revealed a well-developed and well-nourished man who was walking restlessly in acute distress because of severe, steady epigastric pain. He was unable to lie flat on his back, writhing constantly. He felt somewhat better lying on his side, sitting or standing erect. There was no sweating, pallor or cyanosis. The fundi showed "moderate arteriosclerosis." The teeth were carious. The lungs were clear and resonant throughout. The heart was slightly enlarged to the left, the pulse full, 85 per minute, and regular. There was a faint systolic murmur at the apex. The aortic second sound was louder than the pulmonic. The sounds were of good quality. No friction rub was heard. There was marked tenderness, without spasm, high in the midepigastrium, but there were no masses or palpable viscera, and no tympany or abnormal peristalsis. No other positive findings were elicited.

The temperature was 99.8°F., the pulse 85, and the respirations 20. The blood pressure was 180 systolic, 110 diastolic.

Examination of the blood showed a red-cell count of 4,500,000 with 100 per cent hemoglobin, and a white-cell count of 14,300 with 90 per cent polymorphonuclears. The urine and stools were normal. The phenolsulfonphthalein urinary-excretion test showed 25 per cent excretion in fifteen minutes and 60 per cent in one hour. The sedimentation rate ranged between 0.7 and 0.8 mm. per minute. The serum nonprotein nitrogen was 21 mg. per 100 cc. The blood Hinton reaction was negative. An electrocardiogram showed a ventricular rate of 80, with normal rhythm, a PR interval of 0.19 second, diphasic T_1, low T_2 and late inversion of T_4, with left-axis deviation. Roentgenograms of the abdomen with the patient lying down showed one loop of slightly dilated, air-filled small intestine in the left upper quadrant. There was an area of poorly defined decreased density overlying and extending to both sides of the fourth lumbar vertebra. Films in the upright position showed no evidence of free air below the diaphragm. The psoas shadows were clearly outlined. Films of the gall-bladder region with Graham test showed no gallstone. Chest films, both anteroposterior and lateral, revealed a markedly tortuous aorta. Intravenous pyelograms nineteen days after admission showed that there was prompt excretion of poorly concentrated dye on both sides, but the concentration on the right side was not sufficient to outline the kidney pelvis. There were no air-filled dilated loops of bowel. A gastrointestinal series was negative.

For the first four hospital days, the patient ran a slightly elevated temperature (100 to 101°F.), pulse (90 to 95) and respirations (22 to 25), but for the remaining five weeks his chart was flat. The abdominal pain persisted for six days, required heavy morphinization, and then gradually decreased. In this interim, its main focus migrated somewhat from the midepigastrium to the right upper quadrant, and then, as it slowly disappeared, to both lower quadrants. The blood pressures in the arms and legs were about equal at 180 systolic, 100 diastolic. On the fourth and fifth days of the illness, the urine contained 40 and 20 red blood cells per high-power field in the sediment, respectively; thereafter, it was normal. The electrocardiogram on the second hospital day showed low T_1, T_3 and T_4, with slight left-axis deviation, and on the fifth day, low T_1, with a late inversion of T_4. Convalescence was uneventful, and the patient was discharged on the forty-first hospital day.

Second admission (two and a half months later). Following discharge, the patient remained at home on a careful rest regime for six weeks. He then began doing light work, and seemed well until one week before admission, when substernal pain and a sense of chest constriction reappeared, apparently unrelated to exertion, but relieved within half an hour by nitroglycerin.

Physical examination was unchanged from that on the first entry, except that the heart was enlarged 2 cm. beyond the midclavicular line and the blood pressure was 220 systolic, 140 diastolic, in all extremities. The temperature, pulse and respirations were normal. Both urine and blood examinations were negative except for a slightly elevated white-cell count, ranging from 8000 to 13,000. The electrocardiograms were essentially unchanged, but a review of the x-ray films of the chest showed a definite dilatation of the aortic arch when compared with films taken two years previously in the Out Patient Department.

While in the hospital, the patient had a severe one-and-a-half-hour attack of chest pain, which radiated down the left arm and was only partially relieved by morphine. The left radial pulse

was definitely weaker than the right, and the blood pressure in the right arm was 170 systolic, 120 diastolic, whereas that in the left was 120 systolic, 80 diastolic. There were no residual symptoms following this episode. The next day, the blood pressures in the extremities were about equal at 210 to 240 systolic, 150 to 180 diastolic. The patient was discharged on the twenty-fourth hospital day.

Third admission (nine months later). Following discharge, the patient had been well, using nitroglycerin occasionally for chest pain. He had rested for six months, after which he had been doing sedentary work. Twenty-four hours before entry, while working, he experienced the rapid onset of severe pain in the left arm, with an associated mild oppression in the upper sternum and pain on both sides of the neck. This lasted one hour, and one hour later it reappeared. He took a nitroglycerin pill without benefit, and the next day entered the hospital, where an electrocardiogram showed a ventricular rate of 80, with normal rhythm, T_1 inverted, T_2 diphasic, T_3 upright, T_4 inverted, R_4 present and moderate left-axis deviation. Five days later, T_2 was inverted, T_4 more deeply inverted, and T_1 slightly more so. Funduscopic observations revealed several fresh hemorrhages in both fundi. The physical and laboratory findings were otherwise unchanged. The patient remained in the hospital for eight days, during which his chart was normal.

Final admission (four months later). Eight hours before admission, the patient had a sudden attack of substernal pain radiating down both arms and into the neck, following the ingestion of two glassfuls of beer. On examination, he was in obvious pain, breathing rapidly and groaning from time to time. There were a few crackles at the left base posteriorly. The heart sounds were distant and not of good quality; the pulmonary and aortic second sounds were equal. The blood pressure was 194 systolic, 118 diastolic. An electrocardiogram showed no essential change from the last, except biphasic instead of inverted T_1 and T_2. The white-cell count was 15,000. The electrocardiogram two days later showed no change. The patient developed a gallop rhythm, a fall in systolic blood pressure to 158, pallor, sweating and cold extremities, and showed crepitant rales and wheezes at both lung bases, an enlarged slightly tender liver, without edema of the sacrum or the extremities, and distention of the neck veins. He was given oxygen and morphine, and was digitalized. On the third hospital day, he suddenly failed, and died within thirty minutes.

Differential Diagnosis

Dr. Alfred O. Ludwig: In this case, we are confronted with a man who was obviously suffering from hypertension, and we must decide what was the nature of the episodes of severe pain that finally led to his death. Not many conditions cause pain severe enough to be unrelieved by two injections of morphine. One immediately thinks either of extensive cardiac infarction or of some other serious vascular accident. I believe that the radiation of the pain, its character, his efforts "to walk it off" and the occurrence of cramps in the legs are all of great importance in the differential diagnosis.

In the first physical examination, the significant facts are the relatively slow and regular pulse, the apparent fall in blood pressure and the absence of a pericardial friction rub. These findings by no means finally exclude the presence of coronary occlusion. It would be somewhat unusual not to have more shock in the presence of coronary infarction of the severity indicated by the degree of pain that this man had. The absence of spasm in the epigastrium is evidence against such notable peritoneal irritation as would certainly follow any serious abdominal emergency like a ruptured viscus or acute inflammatory disease in this region. The slight elevation of the temperature is quite consistent with either coronary occlusion or any other severe vascular lesion.

The patient had moderate leukocytosis on this admission and a moderately elevated sedimentation rate, and these are of little help in differential diagnosis. The nonprotein nitrogen and renal-function tests indicate that no serious impairment of renal function had yet taken place as a sequel to the hypertension. The changes in the electrocardiogram are consistent with hypertensive heart disease with coronary involvement, but do not indicate the presence of acute occlusion. The x-ray films help us in ruling out a ruptured viscus in that they failed to show gas under the diaphragm, and also dispose of the gall bladder as the seat of this man's symptoms. One would like to know more about this area of decreased density overlying the fourth lumbar vertebra. Was there any evidence of erosion of these vertebras? Could this mass represent dilatation or aneurysm of the abdominal aorta? The tortuosity of the aorta, as demonstrated by the chest films, is a further important point in the differential diagnosis, and further directs suspicion to this vessel. I do not believe that we can draw any valid conclusions from the intravenous pyelograms at this juncture. The gastrointestinal series serves to exclude the stomach as the seat of the lesion.

The most important statements in the next paragraph concern the course of the pain, which continued to be severe for six days, and the appearance of red blood cells in the urine, which suggests to me the possibility that some impairment of renal circulation may have developed. The second electrocardiogram does not convince me that coronary occlusion was present.

The pain returned soon after discharge, this time being more prominent in the chest. Physical examination on the second admission showed a rise in blood pressure over the previous reading. Most significant is the increase in dilatation of the aortic arch in the films taken at that time. The course in the hospital was notable for the occurrence of chest pain, with radiation down the arm, and diminution of the left radial pulse and of the blood pressure in this arm, suggesting impairment of the circulation to this arm, perhaps due to a lesion in the aortic arch.

On the third admission, there had been further extension of the process that had first appeared on the previous occasion and caused a fall in blood pressure in the left arm. The electrocardiogram suggested that there was definite involvement of the coronary tree, and the progressive changes in the T waves strengthen this belief. The fundal hemorrhages may have been secondary to the hypertension or due to interference with circulation. The symptoms on final admission spell further impairment of coronary circulation and rapid heart failure, with pulmonary and hepatic congestion, quickly followed by fatal circulatory collapse.

As I see this case, there is only one condition that satisfactorily explains all the signs and symptoms. I believe that this man had extensive arteriosclerosis of the entire aorta, and that he had successive episodes of dissection of the aortic wall secondary to small rents in the inner coat of this vessel. The first of these I believe took place in the lower thoracic or upper abdominal aorta. The dissection of blood down between the coats of the vessel temporarily interfered with circulation in the legs, as evidenced by the cramps on walking, and later with the renal blood supply, as shown by the appearance of hematuria. The second episode must have involved the aortic arch, with the dissecting blood constricting the mouths of the vessels arising from the arch that supplied the left upper extremity. The third episode may have represented further extension of the dissecting process in the arch to encroach on the coronary mouths and hence leading to coronary insufficiency. Finally, there was further extension in the region of the arch, with further coronary constriction, cardiac collapse and death.

Most of the cases of dissecting aortic aneurysm that we have seen in this hospital have been acute and followed shortly by death. It is quite unusual for this condition to have so long a course as in this man, but such cases have been described. The severe character of the pain and its radiation to the back and shoulders, and later to the neck and arms, are quite characteristic of dissecting aortic aneurysm. When this condition involves the arch or thoracic portion of the vessel, it is commonly confused with coronary occlusion. In such cases, as in this, the absence of the characteristic electrocardiographic changes associated with acute coronary occlusion is a very helpful differential point. When the abdominal aorta is involved, an acute abdominal emergency may be simulated. I believe that the post-mortem examination will disclose the presence of cardiac hypertrophy secondary to the hypertension, extensive sclerosis of the entire aorta, with multiple dissecting aneurysms encroaching on the vessels of the arch, the coronary arteries and possibly the renal arteries. I do not believe that syphilis played any part in the production of the lesion in this case. It is very rare to obtain negative serologic findings in the presence of a syphilitic aortic aneurysm.

Clinical Diagnoses

Acute coronary occlusion.
Hypertensive and coronary heart disease.

Dr. Ludwig's Diagnoses

Essential hypertension.
Hypertensive and coronary heart disease.
Arteriosclerosis of aorta, with dissecting aneurysms of arch and thoracic and abdominal portions of aorta.

Anatomical Diagnoses

Dissecting aneurysms of aorta, old, with rupture into right iliac artery, and fresh, with rupture into pericardium.
Hemopericardium, with cardiac tamponade.
Media necrosis aortica cystica.
Compression of right renal artery, with atrophy of right kidney.
Hypertrophy of left kidney.
Nephritis, chronic vascular.
Cardiac hypertrophy, hypertensive type.
Arteriosclerosis, generalized: marked in aorta and coronary vessels.
Bronchopneumonia, slight, of right lower lobe.

Pathological Discussion

Dr. Tracy B. Mallory: Dr. Ludwig has predicted with great accuracy our post-mortem findings. At the time of the patient's first entry, there was lively discussion in regard to the diagnosis. Several persons, including Dr. Wyman Richardson and Dr. Edward F. Bland, stood out for dissecting aneurysm. A surgical consultant, however, was all for immediate transfer to the Surgical Service and exploratory laparotomy, although he never committed himself on paper to the precise type of surgical abdomen that he expected to find. Dr. Richardson, who was in charge of the service at the time, firmly refused to permit the transfer and remained unshaken in his diagnosis of dissecting aneurysm, even when the patient proceeded to make an unexpected complete recovery. On the second and third admissions, the symptoms were more limited to the cardiac area, and the events of the first admission were lost sight of, so that the final diagnosis on the death report was acute coronary occlusion, associated with hypertensive heart disease. On the final admission, however, Dr. Paul D. White again raised the question of dissecting aneurysm.

At the post-mortem examination, we found two separate dissecting aneurysms, clearly of different ages. The older one, which was obviously responsible for the events leading to the first admission, began with a horizontal tear on the anterosuperior aspect of the arch just distal to the subclavian artery at a point 9 cm. above the aortic valve. This led into smooth, endothelialized fat, which lay within the media of the vessel and nearly, but not quite completely, surrounded the vessel. It had extended downward the entire length of the thoracic and abdominal aorta into the right common iliac artery, where it had ruptured through into the lumen of the latter vessel. This explains the temporary cramps in the right leg and their disappearance with the return of circulation. As evidence of the chronicity of this process, the lumen of the aneurysm was completely endothelialized and was, in fact, dotted with numerous small, bright-yellow plaques of atheroma. A second independent and evidently much more recent dissecting aneurysm began with another horizontal tear of the aortic intima 3 cm. distal to the first one but on the right posterior surface. In this case, the aneurysm had extended backward instead of forward down the ascending aorta to the annulus of the aortic valve, thus involving the mouths of both coronary arteries and that of the innominate artery. Three centimeters above the aortic valve, the outer layer had ruptured into the pericardium, which was distended with 500 cc. of partly clotted blood. This aneurysm was obviously much fresher than the other, since it showed no endothelialization. We did not succeed in finding any trace of a third episode, such as Dr. Ludwig suggested. Therefore, it is quite possible that the dissection of the second aneurysm occurred in more than one stage. It was of interest that the right kidney was only half the size of the left, and the right renal artery seemed considerably narrowed by the external pressure of the aneurysmal fat. The heart, as one would have expected, was considerably hypertrophied, and showed fairly marked atherosclerosis of most of the coronary branches, with numerous patches of narrowing but no foci of occlusion.

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THE RESPONSIBILITIES OF HOSPITALS IN MATTERS OF CIVILIAN DEFENSE

A LARGE majority of the hospitals in Massachusetts have been asked to contribute directly, in one way or another, in the problem of civilian defense. Those that are to be used as emergency hospitals in the event of disaster must provide for adequate supplies and equipment and must so organize their professional and nonprofessional staffs on eight-hour or twelve-hour shifts that teams for the proper care of casualities will be available at a moment's notice. And those that are to serve as base hospitals must be prepared to receive and care for the large numbers of patients who will be evacuated, as soon as possible, from the emergency hospitals. Furthermore, Governor Saltonstall, in his proclamation dated January 8, ordered that "hospitals . . . shall be immediately equipped for blackout." This does not mean that the order applies only to those hospitals that are to be used as emergency and base hospitals but rather to *all hospitals* within the Commonwealth, and the need for such a provision is obvious.

Although much has been asked of the hospitals in the emergency, it is no more than, or as much as, has been demanded of those who work in close association with them. Physicians have willingly responded to calls to military service, to the examining and advisory boards of the Selective Service System, to induction boards, to federal consulting boards and to the central, regional and local organizations of the Medical Division of the Massachusetts Committee on Public Safety. This exemplary response of the medical profession should serve as a pattern for hospital authorities. By promptly and efficiently meeting their responsibilities, they, too, can contribute wisely and effectively to the problems that confront the Commonwealth at this time.

THE SCIENCE OF NUTRITION

THE world will always have to be patient with those who claim, and sympathetic with those who are required, to speak the truth, the whole truth and nothing but the truth, for as Anne Lindbergh observed, "To write or to speak is almost inevitably to lie a little." Our words fit our ideas so loosely. Even the mathematically efficient precision of modern gunnery must be concluded with the phraseology that the marksmanship was "poor" or "good," and in the case of the shell that struck the magazine of the battleship *Hood* the marksmanship was rightly termed "unfortunate." What would William of Orange say to the American columnists who keep repeating that England has not been invaded since the day of William the Conqueror? They have said it so often that many people now believe it to be a fact. Our minds move in tiny circles or leap great gaps of time or space with equal facility. Somehow, we rely on others to keep us from going too far astray.

On whom are we relying to keep our nutritional appraisals and advices within bounds? It is obvious that our nutritional status may not be at an

optimum because nobody knows what the optimum should be. It may even be admitted that there is a serious degree of malnutrition in this country, without throwing too much fat on the fire of the vitamin vendors. The stories of office girls who become listless when they are deprived of their thiamin, however, are reminiscent of the testimonials for Lydia Pinkham's vegetables, or whatever they were. Clinically visible nutritional deficiencies now attract our attention more readily, to be sure, but they are oftener secondary to alcoholism, dementia or advanced organic disease than to a lack of knowledge or economic resource. The gross nutritional lacks of twenty years ago have all but disappeared. What has become of the rickety baby? The adolescents of today are obviously larger and stronger than their parents are or ever were. For a nutritionist[1] to state that our food ways "are worse today than they were in 1914" seems ridiculous. Casual reading of some of his admonitions indicates that we have been going down the wrong road, or even moving backward, but when we see that they are based, among other things, on "many recent nutritional surveys including the extensive governmental study of consumer purchases conducted by the Bureau of Labor Statistics, the Bureau of Home Economics and the National Resources Committee," we begin to see the light.

The Science of Nutrition is being moved into the same apartment with Adequate Medical Care. It can pay the rent; it needs a better home and so is being moved. But it is a large family, which cannot possibly be completely housed even in spacious governmental bureaus; friends and relatives must be left behind who will continue to work under present conditions and with present scientific standards. There is going to be some temptation for those who have acquired new surroundings and new friends to forget their former associates, to forget the standards under which they previously lived and worked. There is going to be some pressure for them to keep up with the Joneses in the new neighborhood, where it is doubtless assumed that diets can be balanced with the same facility as budgets. The House of Delegates of the American Medical Association has called at the new apartment and paid its respects in the form of a series of resolutions adopted at the Cleveland session, but the *Journal of the American Medical Association*[2] has also taken notice of the inspired character of some of the initial efforts. The medical profession may be counted on to back up any statement or program that is warranted by facts or good evidence, or even that is not too greatly exaggerated. Exaggerations, however, are seized on by publicists, who allow their stories to carry unintended implications, and this does the Science of Nutrition no good.

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AN APPRECIATION

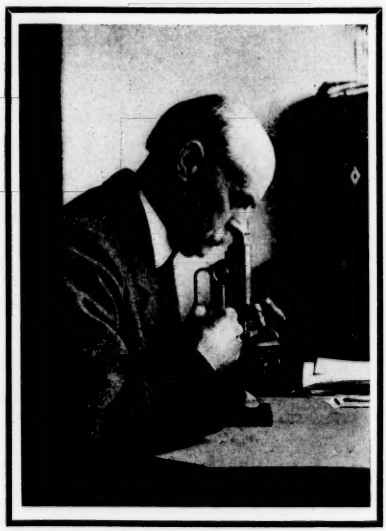
FRANK BURR MALLORY

1862 - 1941

It would appear to be a work of supererogation to discuss the record of Frank Mallory in the city and state that were his for fifty years, and yet he led an almost cloistered existence, which limited the opportunity to meet and know the man. Until the last year of his life, he was doing progressive work in an institute that properly bore his name, since he had demonstrated in his department that a lowly "city hospital" could be made to rival endowed research institutions. It is not my intent to write an obituary but rather an appreciation of a truly great man with whom it was my good fortune to be associated for many years.

One of Dr. Mallory's greatest contributions to the progress of medicine was undoubtedly his work on stains. He spent a year with Ziegler and Chiari in his early days in laboratory medicine, during the period when medical science was coming into flower in the Golden Age of German medicine. As one looks back to that period, it is remarkable to note the coming together of a literal constellation of geniuses, who suddenly appeared and co-operated in the launching of the new scientific medicine. Koch, Abbé, Weigert, Ehrlich and their colleagues, notably the group of fortunate bacteriologists who were in a position to take advantage of the opportunities presented by the new science, were destined to live in medical history.

Ziegler and Chiari were the pathologists of the group, giving special attention to the newer developments of pathologic histology. Weigert had focused attention on the aniline colors, which were an outgrowth from the English Perkins's ink, and microscopic pathology, crude up to then, became a highly specialized field that opened up new vistas in practical medical progress as well as in the field of pure science. Of Dr. Mallory's work in this



FRANK BURR MALLORY

field, Ewing has said, "The older pathologists had largely exhausted the possibilities of pathologic anatomy and histology, but it remained for Mallory, Ramon y Cajal and del Rio Hortega to carry histopathology to its highest development, and to make contributions beyond the reach of other methods."

These masters developed technics by which special tissues could be differentiated through tinctorial reactions. Dr. Mallory's interests began with efforts to more sharply label intercellular substances. Collagen, myoglia and neuroglia fibrils were in his special field of endeavor, and he first demonstrated and described fibroglia fibrils. His next interest was in the application of the new technic to the tracing of origins of cells from embryonal sources, in an effort to classify new growths more exactly. The results of his studies in these and other histologic fields were to revolutionize laboratory practice in America. The laboratory horse-and-buggy period, referred to scornfully by the superior biologic chemist as the "hematoxylin-and-eosine period," was to come to an end. And yet it did not come to an end, or at least hematoxylin did not. Dr. Mallory was among the first to recognize the remarkable character of hematoxylin as a stain. His most selective staining method is that using phosphotungstic acid hematoxylin, and in his later years he was able to develop with hematoxylin a stain for traces of copper in tissues, more delicate than any chemical test. Morphology, banished as a dead subject, has come into its own again in its ability, with tinctorial aids, to do more exacting work than is possible by biochemical methods alone — to identify cells and observe by tinctorial procedures the chemistry of the individual cell.

Dr. Mallory's staining methods were to make his name familiar to laboratory men in all quarters of the globe. The brilliant results obtainable with his stains were arrived at only through exhaustive trial and error until the perfect method was achieved. He would work for months following leads that suggested the possibility of more specific differentiation of tissues or tissue products.

The sheer wizardry that can convert a commonplace coronary lesion, as seen in a section stained with hematoxylin and eosin, into a thing of beauty and distinction, as seen in a section stained by Mallory's aniline blue method, is alluring. It has a touch of Cinderella magic. The lipoid cells cease to be disembodied nuclei and become tangible objects with pink lacelike meshworks enclosing the spaces that had been occupied by the droplets of cholesterol esters. The collagen is a brilliant blue, the fibroglia fibrils are distinct, and the unstriped muscle of the media, bright red, becomes a tissue of quality instead of a bastard relative of the connective-tissue series. The fibrous tissue differentiates itself into young fibroblasts, older collagen-producing cells and frank hyaline scar tissue. With experience, one could almost write the natural history of the lesion without further information.

In this connection, a story told by Elliott Cutler is interesting. Dr. Cutler was working in Krehl's laboratory. The great man made his grand rounds of the laboratory at intervals. The worker stood rigidly at attention, facing his bench and the window, while the professor walked through behind him. If the master condescended to an interest in his work, the student was permitted to unbend and show his wares. Working next to Dr. Cutler was a graduate German student, Professor Marchand's son, who was doing an *Arbeit* on the brain. His sections were poor and badly stained.

Dr. Cutler unearthed in the basement an abandoned paraffin microtome, which was finally coaxed into action. The resulting sections, which were fair, were stained by Mallory's phosphotungstic acid hematoxylin. When the great man made his next visit, he stopped at the student's bench, where he had never stopped before. There were explosive outbursts of *"Wunderbar! Wunderschön!"* as the student explained the provenance of this remarkable exhibit. Dr. Cutler was called on, and told of his work with Dr. Mallory. *"Mallori, Mallori,"* exclaimed the professor, "I thought that he was an Italian."

Dr. Mallory's publications, apart from those on staining technic, were many and varied. His studies cleared the foggy atmosphere that surrounded the complicated pathology of typhoid fever. The paper on this subject, read before the Philadelphia Pathological Society, was illustrated by a series of eight magnificent color plates of drawings that might have served as a model for future medical illustration. However, the cost of such illustrations was almost prohibitive, and they were open to the criticism that, although they represented efforts at objective reproduction by the artist of actual microscopic fields, their delineation by human hands subjected them to possible bias, not with intent, but perhaps as the result of wishful thinking. For these reasons, Dr. Mallory turned to photographic reproductions and, in characteristic fashion, made himself a master of photomicrography. In his publication on the subject with Miss Leavitt, he disclosed the secrets of the art: "The first and greatest secret of good photomicrography is perfect sections, perfectly stained. . . . The second important point is choice of field." How often has he stressed the necessity of spending almost more time on the choice of fields for illustrations than on the writing of a paper! The lessons he taught in this respect resulted in a high quality of illustration in papers by his students, and elevated the level of scientific illustrations in American medical journals.

His studies of typhoid lesions brought out the activities of phagocytic cells, which arose from the endothelium of blood and lymph vessels and which he called endothelial leukocytes. The sources of these cells were widespread, as was their distribution, although the most important origin was the lymph and blood systems of the intestine, the seat of the primary focal infection. In this and further studies, it was recognized that the functions of the endothelial phagocytic cells were distinguished in general from those of the polymorphonuclear leukocytes. Although they did engulf certain bacteria (particularly tubercle bacilli), phagocytosis by the endothelial cells tended to be limited to other cells, particularly red blood cells and lymphocytes.

These studies included observations of mitoses in the endothelium of lymph and blood vessels and the migration of the endothelial leukocytes from the vessels into surrounding tissue. It was further recognized that many of the phagocytic cells passed through the liver and the lungs and thus into the systemic circulation.

Though Metchnikoff had developed his "theory of phagocytes" some years before this time, Mallory's studies of phagocytosis by cells of endothelial origin in human tissues were among the earliest published, were remarkable for their thoroughness of observation, preceded the studies of vital and supravital staining by colloidal dyes, and long antedated the Aschoff concept of the reticuloendothelial system.

The abundant pathologic material from the South Department of the Boston City Hospital was the basis for a series of studies of the pathology of the contagious diseases. A chapter on the pathology of diphtheria was contributed to the Cambridge University *Diphtheria*, edited by Nuttall and Graham-Smith, and papers were written on scarlet fever, measles and whooping cough.

The use of differential stains in determining the embryonal sources of tumor types was thoroughly investigated over a period of years, and the work formed the basis for the Middleton–Goldsmith Lecture of the New York Pathological Society for 1908. This and later papers on the microscopic anatomy and differentiation of cancer established Dr. Mallory's reputation as a national authority on tumors. With Dr. Gaylord, Dr. Weil and a few others, he formed the American Association for Cancer Research. The same group was responsible for stimulating the Congress of American Surgeons to develop interest in the education of the public with reference to cancer. Their action led ultimately to the formation of the American Society for the Control of Cancer.

In 1906, when the Harvard Medical School moved into the new and spacious buildings on Longwood Avenue, Dr. Mallory, under the heading "The Present Needs of the Harvard Medical School," appealed for endowment, not so much for the laboratory branches, although inadequate salaries were preventing men from entering these fields, but for clinical instructors "whose chief interests shall be teaching and scientific medical investigation."

At a time when the older conservative pathologists insisted that the Association of American Physicians was the national pathological society,

Dr. Mallory was one of the leaders in forming the American Association of Pathologists and Bacteriologists and was backed by the younger men in Boston. He took over the *Journal of Medical Research* on the death of Dr. Harold Ernst in 1923, and became its editor-in-chief. When the journal became the *American Journal of Pathology* and was made the official organ of the American Association of Pathologists and Bacteriologists, he remained as its editor-in-chief until 1940.

There arose a demand for a text on laboratory methods, which Dr. Mallory's training and experience and that of his colleague, Dr. Homer Wright, fitted them to satisfy. The familiar *Pathological Technique* was the answer, and has been the accepted authority on the subject since that time. The book represented the result of years of effort in the actual working out of laboratory procedure. With the pathologic material supplied by a large city hospital, supplemented by material from a large semipublic hospital, and added to by problem material referred to him from many sources, it was possible to determine the practical value of standard tests and to develop new procedures, which were improvements on the old or which entered new fields. Under the methods of laboratory study in the Boston City Hospital laboratory, which was early staffed with one or more residents and included a group of graduate students, exhaustive series of applications could be made of a test under investigation. In 1914 was published Dr. Mallory's *Principles of Pathologic Histology*, "which for reliability and detail has never been excelled in any language."

Dr. Mallory took great pride in the technic practiced in his laboratory. He used to refer with a chuckle to the custom of Chiari, who would rap the knuckles of his students if he caught them cutting thin sections. *"Nicht so dünn, nicht so dünn"* was his constant cry. Which reminds one of a famous American expert who is said to have announced, "Give me a good thick section of tissue fixed in formalin and stained with hematoxylin and eosin, and I am content," forgetting the amazing experience and expertness permitting him to make diagnoses under a technical handicap that would floor most if not all his colleagues.

Genius is the infinite capacity for taking pains. No person who was familiar with Dr. Mallory's studies on cirrhosis of the liver could question his tenacity, the exactness of his technic or the thoroughness with which he exhausted all the available experimental fields. His studies of the histology of cirrhosis disclosed the hyaline degeneration of liver cells, which is the distinguishing mark of alcoholic cirrhosis. Because his studies were among the first by modern methods, it was his duty for thirty years to prove that ethyl alcohol was not the cause of the disease. As one genus of animals failed to respond, he turned to others, including many genera that had not before been used for laboratory purposes. He demonstrated, with Parker and Nye, that excess copper was the cause of pigment cirrhosis.

His manner of approach to a study of pathologic processes is illustrated in his introduction to a paper, "Cirrhosis of the Liver: Five different types of lesions from which it may arise." Cirrhosis, which becomes clinically manifest only in its later stages, had been studied almost wholly in its advanced, sclerotic form. Of this tendency, Dr. Mallory said: "In some organs the late stages of certain lesions have received more attention than the beginnings of these lesions. The emphasis has been placed on the wrong end of the process. . . . In order to understand a pathological process, it is necessary to find and study its beginning and to trace its biological development." This paper, beautifully illustrated, was read before the Johns Hopkins Medical Society. More recent studies have not improved on Dr. Mallory's classification of the cirrhoses. He carefully refrained from limiting the causation of cirrhosis to the mechanisms responsible for the five types described. Recent demonstrations of the production of experimental cirrhosis by many agencies justify this caution.

Dr. Mallory lived an ascetic life. His training and experience taught him that the only way to do superlative work was to make that work an obsession, to avoid society and extracurricular demands. It is related that at a faculty function shortly after the birth of his older son, the irrepressible Dr. Arthur ("Patsy") Wentworth arranged with the faculty members that individually they should approach Dr. Mallory with a full glass of champagne and drink the health of the infant, with a hint at bottoms up. It is recorded that Dr. Mallory finished the ordeal with some of its original content of champagne still in his glass.

Austerity is almost a requisite in the public's mental picture of a scientist. To those who did not know Dr. Mallory, he appeared to be a perfect example of the genus, and yet he was intensely human. He had two sons and an army of adoptive sons, to use Sabatini's word, which I like, because it implies mutuality. He was as much interested in the young men who went through his laboratory as though they were his sons. The neophyte who was careless in thought or slovenly in action would feel the sharp edge of his tongue. But, once he had indicated his willingness, his intelligence and his capability, he had

in Dr. Mallory a friend who would help fight his battles. As Dr. Mallory said in his fifty-year class record (1886–1936), "Aside from the problems of my own line of work, one of my greatest pleasures has been in training young men and women in pathology and in seeing what they could make out of themselves under proper encouragement and stimulation; in other words, in getting them to do their own thinking and to work out their own salvation."

Dr. Mallory delivered a Harvey Lecture (1912) ("The Infectious Lesions of Blood Vessels"), the Mellon Lecture for 1925, the Hanna Lecture for 1925 ("Hemochromatosis and Chronic Poisoning with Copper") and the Shattuck Lecture for 1932 ("Cirrhosis of the Liver"). He was awarded the George M. Kober Medal for outstanding service in pathology by the Association of American Physicians. He was the third recipient of the gold-headed cane (following Dr. William H. Welch and Dr. Theobald Smith), given by Dr. Ernst to the American Association of Pathologists and Bacteriologists and awarded by them as a mark of distinguished service. He was a member of the Deutsche Pathologische Gesellschaft and of the Royal Medical Society of Budapest, an honorary member of the Pathological Society of Great Britain and Ireland and a fellow of the American Academy of Arts and Sciences. He was given honorary degrees of Doctor of Science by Tufts College and Boston University. In spite of his many honors, he never posed as a great man and was always available for counsel. The contrast between the autocratic practices in vogue in German laboratories and the procedure in Dr. Mallory's laboratory was great. He "sported his oak" only when some trying bit of experimental work that would not brook interruption was under way. Remarkable to his friends was his ability to turn out progressive research under the constant interruptions that were a part of his daily life.

There was nothing of the "picturesque personality" in his make-up. Dilettantism, with all it implied, was abhorrent to him. He was inclined to be critical in his early days of those whom Weigert called Mr. Modifiers — Jones's modification of Brown's modification of Robinson's stain. He came, however, to appreciate that the modifiers were indicators of the progressive character of scientific medicine. They were emblems of dissatisfaction with things as they were at the moment, and marked a healthy state of discontent. He had great dislike for what he called "armchair pathologists," who capitalized the work of others, or depended on what Wright referred to with a sniff as "closet researches."

Dr. Mallory not only placed his young men in positions for which they were fitted, but followed with fatherly interest their upward progress through the years. And the progress of the men who worked in his laboratory was quite constantly upward. Of professorial rank alone, forty men in American and Chinese schools were or are graduates of the laboratory, and nineteen of them were or are engaged in teaching pathology. Their training in the laboratory fitted them to direct similar work in any medical institution or to start with superior preparation in any of the clinical branches. When plans for a piece of research were in question or difficulties arose in the diagnosis of rare specimens, resort could be had to "The Chief" with assurance of his scientific interest and help. He retained up to the end an undiminished enthusiasm. When something new was brought to him or even something old in the preparation of which good work had been done, his eyes would light up with interest. His critical approval of a piece of original work — the metaphoric tap on the shoulder — was an accolade to be sought for and cherished.

This was a man!

T. L.

MEDICAL EPONYM

Moebius's Sign

The first mention of this sign was made by Moebius in a review of Pierre Marie's *Contribution à l'étude et au diagnostic des formes frustes de la maladie de Basedow* (Paris, 1883). The review appeared in Schmidt's *Jahrbücher der inneren und ausländischen gesammten Medicin* (**200:** 98–100, 1883). A portion of the translation of the former follows:

> Von Graefe has said that lessening or abolition of the synergic movement of the upper lids in raising and lowering the eyes is pathognostic. The reviewer has failed to find Graefe's symptom in a series of cases including some with and some without exophthalmos. He not only disbelieves in its pathognostic character, but considers it rather rare. On the other hand, the reviewer has recently observed a disturbance of convergence in two patients with Basedow's disease, both of whom had a moderate bilateral exophthalmos of equal degree. If the patient was asked to fix his vision on the examiner's finger, both eyes looked to the right or to the left. That is, the patient fixed with one eye, and the external muscles of the other eye contracted consensually. On monocular examination, both internal recti functioned normally. In a third patient with exophthalmos, the symptom was absent. Whether the phenomenon is directly dependent on the exophthalmos is uncertain.

The subject was again discussed, and observations in eight additional cases were reported, in an

article, "Über Insufficienz der Convergenz bei Morbus Basedowii [Convergence Insufficiency in Basedow's Disease]," which was published in the *Zentralblatt für Nervenheilkunde, Psychiatrie und gerichtliche Psychopathologie* (**9**: 356–358, 1886).

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

CAUSES OF MATERNAL DEATH IN MASSACHUSETTS DURING 1940 (*continued*)

ALBUMINURIA, TOXEMIA AND ECLAMPSIA

Twenty-four cases are classified under albuminuria, toxemia and eclampsia.

Undelivered cases. Six patients died undelivered.

Two weeks before term, one patient had a systolic blood pressure of 170, with a large amount of albumin. Hospitalization was advised and refused. The following day, the physician was notified that the patient was having difficulty in breathing. When he arrived, she was dead. Cerebral hemorrhage may have been the immediate cause of death.

Another patient had had no prenatal care, and convulsions were present when she reached the hospital. The systolic blood pressure was over 200. There was a large trace of albumin in the urine. No attempt was made to induce delivery, and the patient died shortly thereafter.

The next case occurred in a twenty-seven-year-old primipara who had had very poor prenatal care. When she arrived in the hospital, she had a blood pressure of 190 systolic, 110 diastolic. She had a large amount of edema. Convulsions appeared, and the patient was treated medically. No attempt at delivery was made.

The next patient, a multipara in her thirteenth pregnancy, had had no prenatal care. The blood pressure was 252 systolic, 152 diastolic. The patient died after receiving a few whiffs of chloroform for an emergency cesarean section.

Another patient died shortly after she reached the hospital. She was comatose when she arrived, and was treated with Veratrone and artificial respiration but never regained consciousness. This patient was very poorly treated during pregnancy. Autopsy showed that the immediate cause of death was hemorrhage about the medulla.

The last patient in this group was a primipara who had had inadequate prenatal care; when she arrived in the hospital, she was in convulsions and unconscious and died within a few hours.

In the cases referred to above, prenatal care was either absent or inadequate. To prevent such fatalities, patients must be taught to visit some physician regularly, and physicians must learn to see their patients regularly and attach more importance than these records show to increased blood pressure and albumin during pregnancy.

Delivered cases. Seventeen patients died after being delivered.

One of these had definite convulsions associated with a separated placenta; she was delivered by the Dublin method but died a few hours later.

Another patient went into labor spontaneously, and was delivered of a child by low forceps but died of eclampsia a few hours later. This patient had grossly inadequate prenatal care.

The next patient had been hospitalized for several weeks and died of a toxemia six hours after a normal delivery.

One patient developed eclampsia after a normal delivery and died two days later.

Another patient was seen frequently by her physician but was not sent into the hospital until convulsions appeared. The blood pressure was 220 systolic, 140 diastolic. She went into labor spontaneously and delivered a stillborn infant. She died five and a half hours after delivery. Although this patient had been frequently seen and apparently intelligently treated, the seriousness of the condition should have suggested the induction of labor much earlier. Had this been done, she probably would not have died.

The next patient, shortly after delivery, had what appeared to be convulsions and a cerebral hemorrhage, from which she did not recover.

One patient, who had been seen routinely during pregnancy and had been treated for syphilis, died eleven hours after delivery, apparently from circulatory collapse. She had had a systolic blood pressure between 150 and 160 and a good deal of albumin in the urine.

Another patient with increased blood pressure and albumin suffered separation of the placenta and died of anuria nine days after delivery.

The next patient was admitted to the hospital in labor. The blood pressure was 180 systolic, 100 diastolic. Following the first convulsion, she was delivered by version, even though the cervix was not fully dilated. The convulsions continued, and death occurred the same day.

One patient was said to have had a fulminating eclampsia. She delivered herself spontaneously and was doing well until three days following delivery, when she suddenly died, presumably of cerebral hemorrhage.

Another patient developed convulsions during

labor. The blood pressure was 176 systolic, 120 diastolic. Five more convulsions developed during the next twelve hours, and death occurred twenty-four and a half hours later.

The next patient, who had a blood pressure of 150 systolic, 130 diastolic, delivered herself of a macerated six months' fetus and presumably was doing well until a week later, when she developed a cerebral hemorrhage and died.

One patient was delivered by low forceps after a normal labor. She had previously shown increased blood pressure and albumin. She was brought into the hospital in coma, after having had a convulsion. There were five convulsions in all, and the patient died shortly after entry.

Another patient developed convulsions before delivery, and died shortly after the birth of twins.

The next patient, who had had excellent care during pregnancy, developed symptoms a week after the blood pressure and urine were normal. She had a separation of the placenta and died of a cerebral hemorrhage.

One patient, who had not been seen at all during pregnancy, had convulsions and did well so far as the toxemia itself was concerned, but died eighteen days later of a complicating pneumonia.

Two cases of toxemia were associated with cesarean section. One patient appeared in the hospital with convulsions. An emergency cesarean section was done, and she died of anuria three days later. An attempt to induce labor by rupturing the membranes was reported in the second case. This was not satisfactory, and since the patient was rapidly failing and labor had not started, a classic cesarean section was done, and she died the following day.

The most striking thing about this series is the number of patients who died of cerebral hemorrhage. There are three cases in which operative treatment can be criticized. The first is that of the patient who was delivered by version before full dilatation. It is believed that if labor does occur, the patient should be left alone until full dilatation, and that she should be allowed to deliver herself if the second stage is not prolonged. The other two are those in which cesarean section was performed. In cases of definite eclampsia, it is agreed that conservative treatment gives far better results.

Transfusion

In 1940, 8 deaths were directly attributed to transfusion. One patient had been delivered by low forceps after a moderately rapid labor, and suffered a moderate post-partum hemorrhage. Transfusion was followed by a reaction within twenty minutes, which was evidenced by a severe chill, an elevation of the pulse rate and lowered blood pressure. The donor and recipient were both in Group IV.

The next case in which incompatible transfusion was the result of death occurred in a woman who had had a severe post-partum hemorrhage associated with an inverted uterus. She had eight blood transfusions, and ultimately died of anuria.

One case occurred in a multipara who had a normal labor when about seven months pregnant and spontaneous delivery of a macerated fetus. She was brought to the hospital a few days later because of secondary anemia and a moderate degree of puerperal sepsis. A transfusion of citrated blood was immediately given, the bloods being typed and cross-matched. Anuria and generalized edema set in, and death occurred twelve days later.

Another case was associated with an operation for rupture in a tubal pregnancy. Transfusion was done following the operation, and suppression of urine immediately set in. The patient died of uremia fifteen days after operation.

The next patient was a primipara, who suffered moderate post-partum hemorrhage following a forceps delivery. On the following day, the hemoglobin was 45 per cent and the red-cell count 2,410,000. Fifteen minutes after a transfusion of citrated blood was started, the patient became weak and complained of loss of vision. Death occurred an hour and a half later.

One case occurred in a patient suffering from mitral stenosis with decompensation. When she was about four months pregnant, therapeutic abortion was performed. Because of hemorrhage, citrated blood from a donor of the same blood group as the patient was started shortly after the operation, but because of cyanosis and a severe chill was stopped after a small amount had been introduced. On the following day, another transfusion with the same blood was completed; death occurred eight hours later.

The next patient who died as a result of transfusion was a primipara who had had a difficult operative delivery. Three hundred and fifty cubic centimeters of blood from a donor of the same group, after direct matching, was administered. The patient became anuric and died forty-eight hours later.

The last case was associated with a transfusion following a cesarean section. Shortly after the transfusion was started, the patient had a severe reaction, and a complete suppression of urine followed. Death occurred two days later.

Although some of these deaths may have involved the Rh factor, — a circumstance whose sig-

nificance is becoming more generally recognized and appreciated, — the fatal outcomes in the majority of cases are inexcusable and clearly point out the need for more carefully and accurately performed compatibility tests.

Pernicious Vomiting

Two patients died as a result of vomiting of pregnancy. One was approximately four months pregnant when pregnancy was interrupted by the introduction of a catheter, in addition to cervical packing. This patient entered the hospital with a temperature of 101°F., and died four days after admission to the hospital.

The other patient, who was sent into the hospital when about three months pregnant, had been vomiting continuously for eight weeks. She was aborted, but death followed.

Both these patients were treated conservatively too long before interference. Modern treatment — consisting of early hospitalization, intravenous therapy and intramuscular thiamin chloride — is so successful that therapeutic abortion is seldom necessary.

Mesenteric Thrombosis

Mesenteric thrombosis was the cause of death in 2 cases. In one of these, the initial abdominal pain came on three hours after normal delivery. Laparotomy was performed thirteen hours later, when the diagnosis of mesenteric thrombosis was confirmed. The patient died forty hours after operation.

The other case of mesenteric thrombosis followed cesarean section. The acute symptoms appeared four days after the patient had been operated on. The patient died twenty-four hours later. The diagnosis was confirmed by autopsy.

These cases are extremely interesting and, fortunately, very unusual.

Sepsis

A more careful review of the deaths in 1940 resulted in the classification of another case in which death was associated with sepsis. This patient had a diaphragmatic hernia; when she was about three months pregnant, it was decided, after medical and surgical consultations, that the hernia would make it unsafe for pregnancy to continue; hence, abortion was advised. No obstetrician saw this patient. An autopsy showed that the patient died of sepsis. The bacteriologic diagnosis was "gas bacillus, hemolytic type."

Surgical Shock

In 1 case, which is still under investigation by a medical examiner, death apparently resulted from surgical shock following a ruptured bladder. The patient was found dead in an apartment house.

TREASURER'S NOTICE

The *New England Journal of Medicine* is sent to all fellows whose dues are fully paid. After March 1, names of delinquent fellows are dropped from the mailing list. All fellows are urged therefore to send, before March 1, their dues for the current year to their district treasurers.

Charles S. Butler, M.D., *Treasurer*

DEATHS

BRAGG — Francis A. Bragg, M.D., of Foxboro, died February 6. He was in his seventy-eighth year.

Born in Shutesbury, Dr. Bragg received his degree from Harvard Medical School in 1894. He was medical examiner for the Sixth Norfolk District and was a member of the Massachusetts Medical Society and the American Medical Association.

He is survived by his widow, a daughter and two sons.

LOURIE — Osip R. Lourie, M.D., of Boston, died recently. He was in his sixty-ninth year.

Born in Russia, Dr. Lourie received his degree from the University of St. Vladimira Faculty of Medicine, Kiev, in 1896. He came to the United States in 1922, and practiced in Boston until his death. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

His widow survives him.

TEN BROECK — Stanton J. Ten Broeck, M.D., of Orange, died January 14. He was in his seventy-first year.

Born in Hillsdale, New York, Dr. Ten Broeck received his degree from New York University Medical College in 1893. He was a member of the Massachusetts Medical Society and the American Medical Association.

He is survived by his widow, a son, three grandchildren and a sister.

WAR ACTIVITIES

UNITED STATES NAVY

The following medical officers of the United States Naval Reserves of the First Naval District have been assigned to active duty outside the First Naval District:

Allen, E. C., Lieut. (JG)

Bean, H. C., Comdr.
Belcher, C. D., Lieut. (JG)
Benson, H. L., Lieut. (JG)
Bigelow, R. B., Lieut. Comdr.
Bird, L. C., Lieut.
Boguniechi, S. J., Lieut. (JG)
Bronstein, B. R., Lieut. (JG)

Carlton, W. T., Lieut. (JG)
Carmody, R. F., Lieut. (JG)
Chamberlain, J. W., Lieut.
Cheever, F. S., Lieut. (JG)
Chesbro, W. L., Lieut.

Cone, T. E., Jr., Lieut. (JG)
Cruickshank, F. S., Lieut. Comdr.
Cummings, G. E., Lieut. (JG)

Farnsworth, D. L., Lieut.
Farrington, R. F., Lieut. (JG)
Feldman, N. N., Lieut. (JG)
Fitzpatrick, W. J., Jr., Lieut. (JG)
Fleischer, H. W., Lieut. (JG)
Forbes, W. W., Lieut. (JG)
Fothergill, L. D., Lieut. Comdr.
Fregosi, H. J., Lieut.

Garrey, W. E., Lieut.
Gauld, A. G., Lieut.
Giuffrida, F., Lieut. (JG)
Glazer, L., Lieut.
Gleason, R. S., Lieut.
Glickman, A. M., Lieut.
Goldblatt, H. W., Lieut. (JG)

Haddad, A. K., Lieut. (JG)
Halbach, R. M., Lieut. Comdr.
Haslam, E. T., Lieut. (JG)
Hayes, J. J., Lieut. (JG)
Helgesson, U. H., Lieut. Comdr.
Herrick, C. A., Lieut. (JG)
Higgins, R. F., Lieut. (JG)
Hinman, H. E., Lieut. (JG)
Hoey, W. O., Lieut.
Hopkins, H. P., Lieut. (JG)

Kepnes, H. A., Lieut. (JG)
Kovarkian, A. V., Lieut.

Leighton, H. T., Lieut. (JG)
Levin, O., Lieut. (JG)
Lowd, H. M., Jr., Lieut. (JG)
Lozner, E. L., Lieut. (JG)
Lulow, W. V., Lieut. (JG)

Marks, H. B., Lieut. (JG)
McLean, E. B., Lieut.
McWilliams, J. G., Lieut. (JG)
Merrill, W., Lieut.
Miller, D. G., Lieut. (JG)
Miller, J. Y., Lieut. (JG)

Nichols, I. C., Lieut. Comdr.
Nunes, J. E., Lieut.

Osterheld, R. G., Lieut.
O'Toole, J. B., Lieut. (JG)

Page, R. S., Jr., Lieut. (JG)
Peters, J. M., Lieut. (JG)
Pippitt, R. B., Lieut. (JG)

Robinson, N. D., Lieut.
Ross, S., Lieut. Comdr.
Rothblatt, B. W., Lieut. (JG)

Schirmer, A. F., Lieut.
Schmidhofer, E., Jr., Lieut. (JG)
Schwab, W. J., Lieut. (JG)
Segal, S. A., Lieut. Comdr.
Shaw, C. C., Lieut. Comdr.
Shaw, E. A., Lieut. (JG)
Smith, E. L., Lieut. (JG)
Smith, K. E., Lieut. (JG)
Sommer, F. X., Lieut. (JG)
Stanbury, J. B., Lieut. (JG)
Stephens, H. F., Lieut. (JG)
Tenney, B. J., Lieut. Comdr.
Truslow, J. B., Lieut. (JG)

Young, V. T., Lieut. (JG)

Zupanec, R., Lieut. (JG)

MISCELLANY

NOTES

Sixteen appointments to the teaching and research staffs of the Harvard Medical School, the Dental School and the new School of Dental Medicine, effective during the present academic year, were recently announced as follows:

Medical School. Edward B. D. Neuhauser, of Cambridge, M.D., University of Pennsylvania '34, instructor in roentgenology; Vincent J. Kelley, of Newton, M.D., Tufts, '25, assistant in laryngology; Sydney Ellis, of Boston, Ph.D., Boston University '41, research fellow in pharmacology; James T. Heyl, of Philadelphia, M.D., Harvard '37, research fellow in medicine; John A. Degen, Jr., of Chestnut Hill, M.P.H., Johns Hopkins '41, assistant in preventive medicine and epidemiology; Frederic W. Rhinelander, II, of Meadowbrook, Pennsylvania, M.D., Harvard '34, assistant in orthopedic surgery; Sam T. Gibson, of Atlanta, Georgia, M.D., Emory University '40, research fellow in medicine; Earl H. Wood, of Philadelphia, Ph.D., University of Minnesota '40, instructor in pharmacology; Gordon J. Axelson, of Chicago, M.D., Duke University '37, assistant in medicine; Donald P. Ham, of Mattapan, M.D., Boston University '38, assistant in roentgenology; Magnus I. Smedal, of Waban, M.D., Harvard '29, assistant in roentgenology; William H. Watters, of Boston, M.D., Boston University '01, instructor in legal medicine; and Victor G. Balboni, of Boston, M.D., Harvard '39, research fellow in medicine.

Dental School. Leonard N. Donsanto, of Brighton, D.M.D., Harvard '38, assistant in oral surgery; and Wallace J. Gardner, of Cambridge, D.M.D., Harvard '39, assistant in roentgenology.

School of Dental Medicine. John W. Cooke, of Boston, D.M.D., Harvard '18, lecturer on clinical dentistry.

The Trustees of Middlesex University announce that at a meeting held on February 9 they appointed Dr. Stephen Rushmore as dean of the School of Medicine, to take office on February 11, 1942.

ANNUAL MORTALITY SUMMARY FOR 1941

The number of deaths in eighty-eight major cities in the United States during 1941 decreased 0.4 per cent as compared with the 1940 figure for the same group of cities on the basis of provisional reports. There were 443,782 deaths reported in 1941 as compared with 445,504 deaths for the corresponding group of cities in 1940.

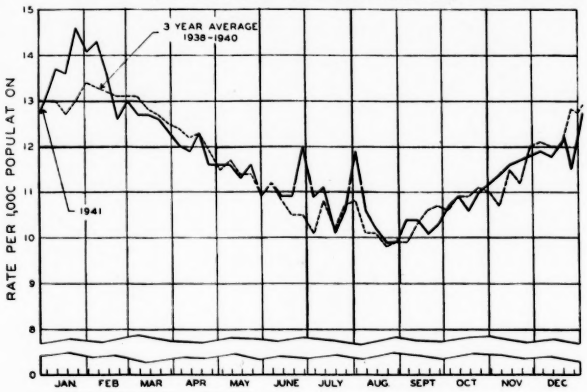
Except for three periods during the year, the weekly death rates for the major cities in the United States in 1941 were generally below those for the average death rates for the three-year period, 1938–1940, inclusive. The first peak in the weekly mortality rates, which occurred in January and February, corresponded with the period of the influenza epidemic (see cut). Two conspicuous in-

creases in mortality rates, in the latter part of June and in early August, were closely related to the heat waves that occurred over a large portion of the country.

The 28,166 infant deaths reported for 1941 represent an increase of 1319, or 4.9 per cent, over the 26,847 infant deaths reported for 1940. However, on the basis of the provisional figures, the infant death rate for 1941 was 36.9 infant deaths per 1000 estimated live births, which represents a decrease of 8.9 per cent as compared with the final mortality rate of 40.5 for 1940.

In the comparison of death rates, it should be noted that the rates are based on the population as enumerated in the 1940 census. Inasmuch as there has been an unusual amount of population movement since the population census was taken, the rates for individual cities need to be interpreted with a certain degree of caution.

DEATH RATE BY WEEKS IN MAJOR CITIES
[RATE BASED ON 1940 ENUMERATED POPULATION]



BOOK REVIEWS

Clinical Immunology, Biotherapy and Chemotherapy in the Diagnosis, Prevention and Treatment of Disease. By John A. Kolmer, M.D., and Louis Tuft, M.D. 8°, cloth, 941 pp., with 27 illustrations, including 11 color plates. Philadelphia: W. B. Saunders Company, 1941. $10.00.

This large and comprehensive volume suffers from the defects common to all textbooks that attempt to cover a vast and rapidly changing field. It is written by two distinguished authorities for the benefit of students and practitioners, and contains a mass of useful, practical information on the technic of performing tests within the scope of ordinary medical practice. There is probably no other book in which such a variety of practical data on the diagnosis, treatment and prevention of every sort of infectious disease is assembled. Because of its all-inclusiveness, the book is spotty. Too much space is devoted to many time-honored methods of treatment that are of dubious value, such as nonspecific protein and vaccine therapy. There are some glaring omissions, such as failure to discuss fever therapy in the section on gonococcal infections. But all in all, this volume represents a conscientious attempt to present to the practicing physician the theoretical and technical knowledge that is essential to the understanding and treatment of infectious disease. Such a book serves a useful function when the biologic and chemotherapeutic armamentarium is so extensive. The work is very much up to date, but in places a more critical appraisal of very recent methods of treatment would be better.

Although this book will not replace a consultant when the life of a patient is at stake, practitioners will find it an extremely useful guide in the handling of patients with all sorts of infectious and allergic conditions.

Medical Diagnosis and Symptomatology. By Samuel A. Loewenberg, M.D. Fifth edition, entirely revised and reset. 4°, cloth, 1139 pp., with 520 illustrations. Philadelphia: F. A. Davis Company, 1941. $12.00.

In the review of the first edition of this book (*New Eng. J. Med.* **201**:199, 1929), attention was called to the fact that the book represented an expansive effort to encompass the field of physical diagnosis and clinical and laboratory medicine within the confines of an ordinary textbook. Although the format and arrangement have been modified, the scope of the book is unchanged. In the opinion of the reviewer, the net result can be summarized as a fair textbook of physical diagnosis that is grossly inadequate in all other respects. The symptoms of lobar pneumonia are described in about eighty words, and those of pulmonary tuberculosis in thirty-six words; and throughout the book, such superficial and sketchy descriptions abound.

Despite the fact that it has now reached the fifth edition, many errors of omission and commission are still noted. Thus, hyperthyroidism is not included in the differential diagnosis of mitral stenosis, and the sharpness of the first heart sound in hyperthyroidism is not mentioned. In describing the duration of the organic murmur, the author states that it "occupies nearly the whole of the systole, diastole or presystole." Under exophthalmos, the pulsating type is omitted. Space does not permit mention of a number of others. What might have been a good textbook of physical diagnosis appears, to the reviewer, to be less than a mediocre book on medicine.

NOTICES

ANNOUNCEMENT

DR. HUGO B. C. RIEMER announces the removal of his Boston office from 128 Newbury Street to 29 Commonwealth Avenue.

BOSTON DOCTORS' SYMPHONY ORCHESTRA

The Boston Doctors' Symphony Orchestra will rehearse, under Alexander Thiede, every Thursday at 8:30 p.m. at Station WMEX, 70 Brookline Avenue, Boston. Those interested in becoming members should communicate with Dr. Julius Loman, 520 Beacon Street, Boston (KEN 3200 or LON 2155).

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of the Peter Bent Brigham Hospital on Tuesday, February 17, at 8:15 p.m.

PROGRAM

Clinical presentation.

The Pathology of Peripheral Neuritis. Dr. Derek Denny-Brown.

Physicians and medical students are cordially invited to attend.

BOSTON LYING-IN HOSPITAL

A meeting of the Journal Club of the Boston Lying-in Hospital will be held at the hospital on Wednesday, February 18, at 8:15 p.m. Dr. Frank Barton, of the Massachusetts Memorial Hospitals, will speak on "The Blood Bank and the Emergency."

Physicians and medical students are cordially invited to attend.

BOSTON SOCIETY OF BIOLOGISTS

A meeting of the Boston Society of Biologists will be held in the Eastman Lecture Room (6-120), Massachusetts Institute of Technology, on Wednesday, February 25, at 8 p.m.

PROGRAM

Serum and Tissue Phosphatase in Experimental Scurvy. Drs. B. S. Gould and H. Schwachman.

The Biological Action of Short Waves: A method for the determination of the local distribution and dosage. Dr. K. S. Lion.

X-ray Diffraction and Electron Microscope Studies of Collagen Fibers. Dr. R. S. Bear, Mr. C. E. Hall, Miss M. A. Jakus and Professor F. O. Schmitt.

After the meeting, there will be a demonstration of the electron microscope and other biophysical apparatus in the Biological Laboratories.

BOSTON MEDICAL HISTORY CLUB

The Boston Medical History Club will hold its fourth meeting of the season at the Boston Medical Library on Wednesday, February 18, at 8:15 p.m. Dr. John Romano will speak on "Early Contributions to the Study of Delirium Tremens."

All interested persons are cordially invited to attend.

MASSACHUSETTS MEMORIAL HOSPITALS

A staff meeting of the Massachusetts Memorial Hospitals will be held in the Evans Memorial Auditorium on Friday, February 27, at 8:15 p.m.

PROGRAM

Report on the Laboratory Department. Dr. Charles F. Branch.

Carcinogenesis as a Conditioned Deficiency. Dr. Cornelius P. Rhoads, director of the Memorial Hospital for Cancer and Allied Diseases, New York City.

JEWISH MEMORIAL HOSPITAL

A diagnostic and therapeutic conference will be held at the Jewish Memorial Hospital on Thursday, February 19, at 11 a. m. Dr. Joseph C. Aub will speak on "Endocrine Problems."

Physicians and medical students are cordially invited to attend.

WALTHAM MEDICAL MEETING

The regular clinicopathological staff conference of the Metropolitan State Hospital will be held at the hospital on Wednesday, February 18, at 8 p.m. Drs. Clementine McKeon and Richard C. Wadsworth will present, "Two Cases of Carcinoma, with Metastases to the Vertebra, Causing Great Pressure and Neurological Complications." Dr. Walter Wegner will lead the discussion.

All interested physicians are cordially invited to attend.

NEW ENGLAND PATHOLOGICAL SOCIETY

There will be a meeting of the New England Pathological Society at the Pathology Amphitheater of the Massachusetts General Hospital on Thursday, February 19, at 8:00 p.m. The exhibit room will be open at 7:30 p.m.

PROGRAM

Exhibit of Pulmonary Surgical Specimens. Drs. R. Klopstock, E. D. Churchill and Benjamin Castleman.

Subdural Abscess: A clinicopathologic study. Drs. C. S. Kubik and R. D. Adams.

Isolation of Pleuropneumonia-Like Organisms from Human Patients. Drs. W. E. Smith and L. Dienes.

The Nature of Pleuropneumonia-Like Organisms. Dr. L. Dienes.

Renal Biopsies from Hypertensive Patients. Dr. Benjamin Castleman.

Business meeting.

Collation.

NEW ENGLAND HEART ASSOCIATION

A meeting of the New England Heart Association will be held in the Evans Memorial on Wednesday, *February 25*, at 8:15 p.m. It should be noted that the date has been changed from that originally announced.

PROGRAM

Effect of Venous Obstruction on Blood Flow in the Limbs. Drs. C. K. Friedland and R. W. Wilkins.

Congenital Mitral Stenosis and Atresia. Dr. A. S. Nadus.

Blood and Cell-Volume Determinations with Radioactively Tagged Erythrocytes. Drs. J. F. Ross and M. A. Chapin.

Ultimate Effect of Pregnancy on Rheumatic Heart Disease. Dr. N. H. Boyer.

Some Remarks Concerning the Clinical Diagnosis of Pulmonary Embolism and Infarction. Dr. Chester S. Keefer.

Interested physicians and medical students are cordially invited to attend.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

A regular meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore, Boston, on Wednesday, February 18, at 8 p.m. Dr. John H. Talbott will speak on "Physiologic and Therapeutic Effects of Hypothermia." Dr. Augustus Rose will lead the discussion. A council meeting will be held at 6 p.m., followed by an informal dinner in the Empire Room at 6:30.

All interested physicians are cordially invited to attend the meeting.

HEMATOLOGY JOURNAL CLUB

There will be a meeting of the Hematology Journal Club at the Joseph H. Pratt Diagnostic Hospital, Thursday, February 26, at 8:15 p.m.

PROGRAM

Discussion of cases.

Discussion of sickle-cell anemia.

Physicians and medical students are cordially invited to attend.

AMERICAN CONGRESS ON OBSTETRICS AND GYNECOLOGY

The second American Congress on Obstetrics and Gynecology will be held in St. Louis, Missouri, April 6 to 10, 1942. All the meetings and the commercial, educational and scientific exhibits will be held in the Public Auditorium.

The general plan for the program will be much the same as that of the first congress, which was held in Cleveland in 1939, with sectional meetings for the various groups (nurses, public-health officers, administrators, educators and physicians), general sessions for all members attending the congress and round-table discussions. The evening sessions will be open to the general public.

Admission to the congress will be by membership cards only, which may now be secured by the payment of a $5.00 registration fee. All mail should be addressed to and further information may be obtained from the American Congress on Obstetrics and Gynecology, 650 Rush Street, Chicago.

UNITED STATES CIVIL SERVICE EXAMINATION

Orthopedic Mechanics

An examination has been announced by the Civil Service Commission to secure orthopedic mechanics for the Army services. The salary is $2000 a year. Persons may qualify under the following optional subjects: General, bracemaker, shoemaker and leatherworker, and limbmaker. Because of the demand for qualified eligibles, applications will be accepted at the Commission's Washington office until further public notice.

Persons appointed will construct, design, alter and repair orthopedic appliances as indicated by the optional subjects. This includes working from living models and plaster casts, doing nickel plating, and shaping, grinding, and polishing metals used in orthopedic appliances.

Applicants will not take a written test, but will be rated on the extent and quality of their experience. They must have had five years of appropriate experience in orthopedic work within the past ten years. Under the option "shoemaker and leatherworker," persons whose experience has been in general shoe repair will not be considered qualified.

Examination announcements and application forms may be obtained at first-class and second-class post offices and from the Civil Service Commission, Washington, D. C.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING SUNDAY, FEBRUARY 15

MONDAY, FEBRUARY 16

12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital amphitheater.

TUESDAY, FEBRUARY 17

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. Chemotherapy. Dr. Maxwell Finland. South End Medical Club. Headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston.

12:15–1:15 p.m. Clinicoroentgenologic conference. Peter Bent Brigham Hospital amphitheater.

8:15 p.m. Pathology of Peripheral Neuritis. Dr. Derek Denny-Brown. Harvard Medical Society. Peter Bent Brigham Hospital amphitheater.

WEDNESDAY, FEBRUARY 18

*9:00–10:00 a.m. Recent Advances in Allergy. Dr. E. A. Brown. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. Clinicopathological conference. Children's Hospital.

12:00 m. The X-ray in Diseases of the Digestive Tract and Biliary System. Dr. Samuel A. Robins and his associates. Boston Gastroenterological Society. Beth Israel Hospital.

*8:00 p.m. Physiologic and Therapeutic Effects of Hypothermia. Dr. John H. Talbott. New England Society of Physical Medicine. Hotel Kenmore, Boston.

*8:15 p.m. Early Contributions to the Study of Delirium Tremens. Dr. John Romano. Boston Medical History Club, Boston Medical Library.

*8:15 p.m. The Blood Bank and the Emergency. Dr. Frank Barton. Boston Lying-in Hospital.

*8:30 p.m. The Use of Drugs in the Treatment of Alcoholism. Dr. Wilfred Bloomberg. Washingtonian Hospital.

THURSDAY, FEBRUARY 19

*9:00–10:00 a.m. Medical clinic. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*11:00 a.m. Endocrine Problems. Dr. Joseph C. Aub. Jewish Memorial Hospital.

8:00 p.m. New England Pathological Society. Massachusetts General Hospital.

FRIDAY, FEBRUARY 20

*9:00–10:00 a.m. Clinical and Experimental Observations on the Use of Thyrothricin in the Treatment of Infections. Dr. C. H. Rammelkamp. Joseph H. Pratt Diagnostic Hospital.

SATURDAY, FEBRUARY 21

*9:00–10:00 a.m. Sulfur Metabolism. Dr. Martin Nothmann. Joseph H. Pratt Diagnostic Hospital.

*Open to the medical profession.

FEBRUARY 18. Waltham Medical Meeting. Page 289.

FEBRUARY 19–21. American Orthopsychiatric Association. Page 708, issue of October 30.

FEBRUARY 20–21. New York University College of Medicine. Page ix, issue of January 29.

FEBRUARY 25. Boston Society of Biologists. Page 289.